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Vol. 47—No. 101

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# federal register

**Book 1 of 2 Books**
**Tuesday, May 25, 1982**

## Selected Subjects

**Air Pollution Control**
Environmental Protection Agency

**Alcohol and Alcoholic Beverages**
Alcohol, Tobacco and Firearms Bureau

**Animal Drugs**
Food and Drug Administration

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National Oceanic and Atmospheric Administration

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Food and Drug Administration

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Food and Nutrition Service

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# Selected Subjects

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**Editor's Note:**

The list of subjects on the cover is designed to assist those users who review the **Federal Register** for broad subject areas. The list is compiled from subject terms supplied by agencies for certain of their rule and proposed rule documents as required by 1 CFR 18.20. Subject terms in the list may refer to more than one document. To locate the documents in the **Federal Register** covered by the subject terms in the list, users should consult the Table of Contents under the appropriate agency. We remind users that the list is a selective supplement to the Table of Contents and should not be construed as comprehensive.

This list is an experiment. We hope it will prove useful to those users inconvenienced by the discontinuation of the "Highlights" in February because of reduced personnel resources at the Office of the Federal Register. For this new list our editors simply select subject terms from those appearing in the edition's rule and proposed rule documents rather than perform the detailed analytical work which was needed to produce the "Highlights".

Comments on this list may be sent to Martha Girard, Director, Executive Agencies Division (NFE), Office of the Federal Register, NARS/GSA, Washington, D.C. 20408. Phone (202) 523-5240 (not a toll free number).

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## CFR PARTS AFFECTED IN THIS ISSUE

A cumulative list of the parts affected this month can be found in the Reader Aids section at the end of this issue.

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# Presidential Documents

Title 3—

The President

## Presidential Determination No. 82-12 of April 8, 1982

## Eligibility of Antigua and Barbuda To Make Purchases of Defense Articles and Defense Services Under the Arms Export Control Act

**Memorandum for the Honorable Alexander M. Haig, Jr., the Secretary of State**

Pursuant to the authority vested in me by Section 3(a)(1) of the Arms Export Control Act, I hereby find that the furnishing of defense articles and defense services to the Government of Antigua and Barbuda will strengthen the security of the United States and promote world peace.

You are directed on my behalf to report this finding to the Congress.

This finding shall be published in the **Federal Register.**

Ronald Reagan

THE WHITE HOUSE,
*Washington, April 8, 1982.*

[FR Doc. 82-14320
Filed 5-21-82; 4:39 pm]
Billing code 3195-01-M

# Presidential Documents

**Executive Order 12363 of May 21, 1982**

## The Foreign Service of the United States

By the authority vested in me as President by the Constitution and laws of the United States of America, including the Foreign Service Act of 1980 (94 Stat. 2071, 22 U.S.C. 3801 *et seq.*),* Section 202 of the Revised Statutes (22 U.S.C. 2656), and Section 301 of Title 3 of the United States Code, and in order to further provide for the administration of the Foreign Service of the United States, it is hereby ordered as follows:

**Section 1.** Executive Order No. 12293 of February 23, 1981 (46 FR 13969), is amended by adding the following new sections:

"Sec. 9. (a) Pursuant to Section 210 of the Act there is established in the Department of State the Board of the Foreign Service (22 U.S.C. 3930).

"(b) The Board shall be composed of the designated number of representatives of the heads of the following agencies:

"(1) Department of State, four members, at least three of whom must be career members of the Senior Foreign Service;

"(2) International Communication Agency, two members, one of whom must be a career member of the Senior Foreign Service;

"(3) United States International Development Cooperation Agency, two members, one of whom must be a career member of the Senior Foreign Service;

"(4) Department of Agriculture, two members, one of whom must be a career member of the Senior Foreign Service;

"(5) Department of Commerce, two members, one of whom must be a career member of the Senior Foreign Service;

"(6) Department of Labor, one member;

"(7) Office of Personnel Management, one member;

"(8) Office of Management and Budget, one member; and,

"(9) Equal Employment Opportunity Commission, one member;

"(c) The membership of the Board shall be selected from among officials who are knowledgeable in matters concerning the management of the Foreign Service. Except for the career members of the Senior Foreign Service from the Department of Agriculture, the Department of Commerce, the International Communication Agency, and the United States International Development Cooperation Agency, the members of the Board shall be selected from among those who have the rank of Assistant Secretary or higher or a position of comparable responsibility.

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The correct citation is 22 U.S.C. 3901 *et seq.*

"(d) The Secretary of State may from time to time request the heads of other agencies to designate representatives to participate in the functions of the Board on a regular or occasional basis.

"(e) The Secretary of State shall designate a Chairman of the Board from among those members who are career members of the Senior Foreign Service.

"(f) The Secretary of State shall provide all necessary administrative services and facilities for the Board.

"Sec. 10. Pursuant to Section 202(a)(2)(B) and (a)(3)(B) of the Act (22 U.S.C. 3922(a)(2)(B), (a)(3)(B)), it is hereby determined to be necessary, in order to enable the Department of Agriculture and the Department of Commerce to carry out functions which require service abroad, for the respective Secretaries, in consultation with the Office of Personnel Management and the Office of Management and Budget, to be able to utilize the Foreign Service personnel system with respect to personnel of the following:

"(a) The Animal and Plant Health Inspection Service of the Department of Agriculture, not to exceed 125 positions, without the prior approval of the Director of the Office of Personnel Management;

"(b) The United States Travel and Tourism Administration, and the International Trade Administration of the Department of Commerce, not to exceed 30 positions without the prior approval of the Director of the Office of Personnel Management, and providing that assignments to such positions be administered consistent with policies of the Foreign Commercial Service established under Executive Order No. 12188.".

**Sec. 2.** In Section 8 of Executive Order No. 12293, the phrase "This Order" is amended to read "The first seven Sections of this Order".

**Sec. 3.** Executive Order No. 11264 of December 31, 1965, as amended, is revoked.

Ronald Reagan

THE WHITE HOUSE,
*May 21, 1982.*

[FR Doc. 82-14321
Filed 5-21-82; 4:40 pm]
Billing code 3195-01-M

# Rules and Regulations

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## DEPARTMENT OF AGRICULTURE

### Agricultural Marketing Service

### 7 CFR Part 953

### Irish Potatoes Grown in the Southeastern States; Handling Regulation

**AGENCY:** Agricultural Marketing Service, USDA.

**ACTION:** Final continuing rule.

**SUMMARY:** This continuing regulation requires fresh market shipments of potatoes grown in designated counties of Virginia and North Carolina to be inspected and meet minimum grade and size requirements. It should promote orderly marketing of such potatoes and keep less desirable qualities and sizes from being shipped to consumers.

**EFFECTIVE DATE:** June 5, 1982.

**FOR FURTHER INFORMATION CONTACT:** Charles W. Porter, Chief, Vegetable Branch, F&V, AMS, USDA, Washington, D.C. 20250 (202) 447-2615. The Final Impact Statement relating to this final rule is available upon request from Mr. Porter.

**SUPPLEMENTARY INFORMATION:**

#### Paperwork Reduction Act

Information collection requirements contained in this regulation (7 CFR Part 953) have been approved by the Office of Management and Budget under the provisions of 44 U.S.C. Chapter 35 and have been assigned OMB No. 0581-0084.

This final rule has been reviewed under Secretary's Memorandum 1512-1 and Executive Order 12291 and has been designated a "nonmajor" rule. William T. Manley, Acting Administrator, Agricultural Marketing Service, has determined that this action will not have a significant economic impact on a substantial number of small entities because it would not measurably affect costs for the directly regulated handlers.

Marketing Agreement No. 104 and Order No. 953, both as amended, regulate the handling of potatoes grown in designated counties of Virginia and North Carolina. This program is effective under the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601-674). The Southeastern Potato Committee, established under the order, is responsible for its local administration.

Notice of rulemaking was published in the April 23, 1982, **Federal Register** (47 FR 17528). The notice afforded interested persons through May 10, 1982, to file written comments on the proposal. No comments were received.

This regulation is based upon recommendations made by the committee at its public meeting in Norfolk, Virginia, on April 1, 1982.

The grade and size requirements are the same as those which have been issued during past seasons. They are necessary to prevent potatoes of poor quality or undesirable sizes from being distributed to fresh market outlets. The regulation will benefit consumers and producers by standardizing and improving the quality of the potatoes shipped from the production area.

Again this season the minimum quantity exemption will be five hundred-weight. This should relieve the burden on handling noncommercial quantities of potatoes and allow direct marketing outlets to operate in greater freedom.

Exceptions are provided to certain of these requirements to recognize special situations in which such requirements would be inappropriate or unreasonable.

Shipments will be allowed to certain special purpose outlets without regard to the grade, size, and inspection requirements provided that safeguards are met to prevent such potatoes from reaching unauthorized outlets. Shipments for use as livestock feed will be so exempt because requirements for this outlet differ greatly from those for fresh market. Since no purpose would be served by regulating potatoes used for charity purposes, such shipments also will be exempt. Also, potatoes for most processing uses are exempt under the legislative authority for this part.

This regulation promotes efficiency by standardizing marketing practices and will have no measurable effect on the quantity of potatoes shipped from Virginia and North Carolina or upon U.S. retail potato prices. It should enable the Southeastern potato industry to better compete with other potato producing areas in the U.S. by ensuring the use of grades and sizes acceptable to buyers.

Therefore, after consideration of all relevant matters, including the proposal in the notice, it is found that the following handling regulation will tend to effectuate the declared policy of the act by setting the minimum grade, size and inspection requirements which the Secretary has found should be maintained for orderly marketing.

It is further found that good cause exists for not postponing the effective date of this section until 30 days after its publication in the **Federal Register** (5 U.S.C. 553) in that (1) shipments of potatoes grown in the production area will begin on or about the effective date of June 5, 1982, (2) to maximize benefits to producers, the regulation should apply to as many shipments as possible during the marketing season, and (3) handlers under this part should be able to complete by June 5, 1982, all preparations to comply with the regulation, which is similar to those of previous marketing seasons.

Requirements contained in this handling regulation, effective June 5, 1982, will continue in effect from marketing season to marketing season indefinitely unless modified, suspended, or terminated by the Secretary upon recommendation and information submitted by the committee or other information available to the Secretary. Heretofore, regulations issued under the marketing order were effective for a single marketing season. However, the same requirements have been imposed each season since 1969. The change to issue regulations which will continue in effect from marketing season to marketing season reflects the fact that regulations will probably continue to change infrequently from season to season and it is believed unnecessary to issue them for only a single season. In addition, the change could result in a reduction in operational costs to the committee and the government. Although the final regulation will be effective for an indefinite period, the committee will continue to meet prior to or during each season to consider recommendations for modification,

suspension, or termination of the regulation. Prior to making any such recommendations, the committee will submit to the Secretary a marketing policy for the season in accordance with § 953.40 of the order, including an analysis of supply and demand factors having a bearing on the marketing of the crop. Committee meetings are open to the public and interested persons may express their views at these meetings or may file comments with the Hearing Clerk until May 20 each year. The Department will evaluate committee recommendations and information submitted by the committee, comments filed, and other available information, and determine whether modification, suspension, or termination of the regulations on shipments of Southern potatoes would tend to effectuate the declared policy of the act.

**List of Subjects in 7 CFR Part 953**

Marketing agreements and orders, Potatoes, Virginia, North Carolina.

## PART 953—IRISH POTATOES GROWN IN SOUTHEASTERN STATES

**§ 953.321 [Removed]**

Section 953.321 (46 FR 29453, June 2, 1981, and 46 FR 30487, June 9, 1981) is removed and a new § 953.322 is added as follows:

**§ 953.322 Handling regulation.**

During the period beginning June 5 and ending July 31 each season no person shall ship any lot of potatoes produced in the production area unless such potatoes meet the requirements of paragraphs (a) and (b) of this section or unless such potatoes are handled in accordance with paragraphs (c) and (d) or (e) of this section.

(a) *Minimum grade and size requirements.* All varieties U.S. No. 2, or better grade, 1⅛ inches (38.1mm) minimum diameter.

(b) *Inspection.* Except as provided in paragraphs (c) and (e), no handler shall ship any potatoes unless an appropriate inspection certificate covering them has been issued by the Federal-State Inspection Service and the certificate is valid at the time of shipment.

(c) *Special purpose shipments.* The grade, size, and inspection requirements set forth in paragraphs (a) and (b) of this section shall not apply to potatoes shipped for canning, freezing, "other processing" as hereinafter defined, livestock feed or charity, except that the handler of them shall comply with the safeguard requirements of paragraph (d) of this section.

(d) *Safeguards.* Each handler making shipments of potatoes for canning, freezing, "other processing," livestock feed, or charity in accordance with paragraph (c) of this section shall:

(1) Notify the committee of the handler's intent to ship potatoes pursuant to paragraph (c) of this section by applying forms furnished by the committee for a Certificate of Privilege applicable to such special purpose shipments;

(2) Obtain an approved Certificate of Privilege;

(3) Prepare on forms furnished by the committee a special purpose shipment report for each such individual shipment; and

(4) Forward copies of such special purpose shipment report to the committee office and to the receiver with instructions to sign and return a copy to the committee's office. Failure of the handler or receiver to report such shipments by promptly signing and returning the applicable special purpose shipment report to the committee office shall be cause for suspension of such handler's Certificate of Privilege applicable to such special purpose shipments.

(e) *Minimum quantity exemption.* Each handler may ship up to, but not to exceed, five hundredweight of potatoes any day without regard to the inspection and assessment requirements of this part, but this exception shall not apply to any portion of a shipment that exceeds five hundredweight of potatoes.

(f) *Definitions.* The term "U.S. No. 2" shall have the same meaning as when used in the U.S. Standards for Grades of Potatoes as amended (7 CFR 2851.1540–2851.1566), including the tolerances set forth in it. The term "other processing" has the same meaning as the term appearing in the act and includes, but is not restricted to, potatoes for dehydration, chips, shoestrings, starch, and flour. It includes only that preparation of potatoes for market which involves the application of heat or cold to such an extent that the natural form or stability of the commodity undergoes a substantial change. The act of peeling, cooling, slicing, dicing, or applying material to prevent oxidation does not constitute "other processing." All other terms used in this section shall have the same meaning as when used in Marketing Agreement No. 104 and this part, both as amended.

(g) *Applicability to imports.* Pursuant to section 8e of the act and § 980.1 "Import regulations" (7 CFR 980.1), Irish potatoes of the round white type imported during the effective period of this section shall meet the grade, size, quality, and maturity requirements specified in paragraph (a) of this section.

(Secs. 1–19, 48 Stat. 31, as amended; 7 U.S.C. 601–674)

Dated May 20, 1982 to become effective June 5, 1982.

Russell L. Hawes,

*Acting Deputy Director, Fruit and Vegetable Division, Agricultural Marketing Service.*

[FR Doc. 82-14230 Filed 5-24-82; 8:45 am]

BILLING CODE 3410-02-M

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## Commodity Credit Corporation

## 7 CFR Part 1421

**[Amdt. 2]**

## Standards for Approval of Warehouses for Grain, Rice, Dry Edible Beans, and Seed

**AGENCY:** Commodity Credit Corporation, USDA.

**ACTION:** Final rule.

**SUMMARY:** The purpose of this final rule is to amend Commodity Credit Corporation (CCC) regulations governing Standards for Approval of Warehouses for Grain, Rice, Dry Edible Beans, and Seed, which are owned by CCC or which are serving as collateral for a price support loan issued by CCC. This final rule amends the regulations: (1) To prescribe the manner by which warehousemen must submit financial statements and financial records to CCC; (2) to increase a certain rate used to calculate net worth requirements; (3) to delete the $250,000 net worth ceiling applicable to warehousemen; and (4) to permit warehousemen to furnish an irrevocable letter of credit to CCC as security to satisfy any deficiency in the net worth requirement. The purpose of this rule is to insure greater security for CCC in its use of warehouses approved by CCC for storage of commodities.

**EFFECTIVE DATE:** July 1, 1982.

**FOR FURTHER INFORMATION CONTACT:** Barry W. Klein, Marketing Specialist, U.S. Department of Agriculture, Agricultural Stabilization and Conservation Service, Transportation and Storage Division, Storage Management Branch, P.O. Box 2415, Washington, D.C. 20013; (202) 447-7911. The Final Regulatory Impact Analysis describing the options considered in developing the final rule and the impact implementing each option is available upon request.

**SUPPLEMENTARY INFORMATION:** This final rule has been reviewed under USDA procedures and Executive Order 12291 and Secretary's Memorandum No. 1512-1 and has been classified "not major". This rule has been classified "not major" since it does not result in:

(1) An annual effect on the economy of $100 million or more; (2) a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographical regions; or (3) significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or export markets.

This rule will not have a significant impact specifically on area and community development. Therefore, review as established by OMB Circular A-95 was not used to assure that units of local governments are informed of this action.

It has been determined that the Regulatory Flexibility Act is not applicable to this final rule since CCC is not required by 5 U.S.C. 553 or any other provision of law to publish a notice of proposed rulemaking with respect to the subject matter of this rule.

The Commodity Credit Corporation Charter Act (15 U.S.C. 714) authorizes CCC to conduct various activities to stabilize, support, and protect farm income and prices. CCC is authorized to carry out such activities as making price support available with respect to various agricultural commodities, removing and disposing of surplus agricultural commodities, exporting or aiding in the exportation of agricultural commodities, and procuring agricultural commodities for sale both in the domestic market and abroad. Section 4(b) of the CCC Charter Act provides that the Corporation shall not acquire real property in order to provide storage facilities for agricultural commodities, unless CCC determines that private facilities for the storage of such commodities are inadequate. Further, Section 5 of the CCC Charter Act provides that in carrying out the Corporation's purchasing and selling operations, and in the warehousing, transporting, processing or handling of agricultural commodities, CCC is directed to use, to the maximum extent practicable, the usual customary channels, facilities, and arrangements of trade and commerce.

Accordingly, CCC has set forth Standards for Approval of Warehouses which must be met by warehousemen before CCC will enter into storage agreements with such warehousemen for the storage of agricultural commodities which are owned by CCC or which are serving as collateral for CCC price support loans.

In the last several years, the risk to depositors of grain in warehouses has increased due to changes in the marketing operations of warehousemen who are buying and selling grain. The use of "delayed price" and "deferred payment" contracts has contributed to the possibility of increased losses to grain depositors. The increase in grain warehouse bankruptcies over the past several years has demonstrated a need to amend the Standards for Approval of Warehouses to compensate for the changes in grain marketing.

Accordingly, a notice of proposed rulemaking was published by the Department in the **Federal Register** on October 13, 1981, (46 FR 50378-80) requesting comments with respect to a number of proposals regarding changes in the Standards for Approval of Warehouses for Grain, Rice, Dry Edible Beans, and Seed. The initial comment period ended November 16, 1981. The comment period was subsequently extended to December 16, 1981.

The proposed changes in the regulations would require a warehouseman to furnish to CCC an annual financial statement which has been examined by an independent Certified Public Accountant (CPA). In addition, the warehouseman would be required to submit to CCC a copy of the CPA audit report, prepared in accordance with generally accepted auditing standards, of the financial statement of such warehouseman. Also the regulations would be amended (1) to delete the requirement that the net worth of the warehouseman need not exceed $250,000, and (2) to increase the rate used in calculating the net worth requirement of grain warehouses from 10 cents to 20 cents per bushel. Additionally, it was proposed that the Standards be amended to permit the warehousemen to furnish to CCC an irrevocable letter of credit as security to meet any deficiency in net worth provided the issuing bank was an insured commercial bank in the United States with assets of $100 million or more. The following is a discussion of the comments received with respect to the proposed changes in the regulations.

**Submission of a Financial Statement Audited by an Independent Certified Public Accountant**

There were a total of 273 responses to the proposed rule regarding the CPA audit. Responses were from grain commission companies, grain terminals, country elevator operators, grain and feed associations, CPA firms, licensed public accountant firms, elevator associations, cooperative marketing associations, State Departments of Agriculture, cooperative associations, and members of Congress.

Seven respondents favored the requirement that there be submitted a financial statement, examined by an independent CPA, accompanied by a copy of the CPA's audit report prepared in accordance with generally accepted auditing standards. These respondents felt that the CPA audit would: (1) Provide an independent certification of the status of the grain inventory and related storage obligation; (2) assist management of the warehouse by highlighting opportunities and problem areas; and (3) give CCC and the warehouseman an early signal of possible failures of the warehouse operation.

Respondents not favoring the CPA proposal total 265. The basic objections to requiring a CPA audit were as follows: (1) The added overhead resulting from CPA audits costs would be eventually charged to the customer (producers and CCC) without fully accomplishing the desired goal; (2) some warehousemen may not renew their Uniform Grain Storage Agreement (UGSA) if they are required to furnish a CPA audited financial statement; (3) there are not enough qualified CPA's with grain measurement, warehousing, and merchandising experience available to perform the required service; (4) requiring a CPA audit will not prevent a firm from filing for bankruptcy or ensure financial responsibility; (5) in many cases, commission houses already monitor the overall operation of the country warehouse and provide quarterly and annual audits of grain inventories and storage obligations to ensure the financial stability of the warehouse; (6) CPA audits could cause significantly less participation in the UGSA program, thus resulting in less available storage space, less competition among warehouses, and higher storage rates to the government; (7) if a large number of elevator operators discontinued their UGSA, CCC would lose much of the control it now has in reviewing elevator operations; and (8) it would be inconvenient for farmers if warehousemen cancel their UGSA thus forcing farmers to transport their grain which is serving as collateral for a regular or grain reserve loan to distant locations for storage.

Several alternatives and options were offered in lieu of a financial statement audited by an independent CPA. There were several suggestions that CCC permit the submission of an annual

review of financial conditions of a warehouseman. It was suggested the CCC permit an audit or review of a warehouseman to be completed by a licensed public accountant. Another suggestion was to increase the net worth requirement and require a performance bond from warehousemen. A third suggested alternative was to permit the warehouseman to provide a management-verified financial statement. A management-verified financial statement would be prepared in accordance with generally accepted auditing standards without independent audit verification. It was further suggested that a financial statement of the warehouseman should be filed by the chief executive officer of the warehouse who would personally verify that the financial statement accurately reflects the financial condition of the warehouse. It was also suggested that CCC accept a financial statement that has been compiled and reviewed by an agent of the warehouseman (e.g., a grain commission house). Several of those commenting suggested that CCC require that a financial statement be audited by a certified or licensed public accountant and that the audit include:

1. A balance sheet;

2. An income statement which includes annual gross sales of commodities;

3. A statement of changes in financial position; and

4. A footnote or schedule disclosure of:

a. The total bushels/pounds received annually by commodity;

b. The amount of commodity in storage at end of year;

c. The amount of each commodity held for depositors;

d. The amount of farm stored grain contracted for but not delivered;

e. The amount of each commodity sold but not shipped; and

f. Any new crop purchases and sales of a commodity.

After careful consideration of the comments presented, both written and verbal, it has been determined that the changes contemplated in the proposed rule will be modified based upon a number of the alternatives which were submitted in the comments. The financial statement requirements as presented in this final rule will give flexibility to the warehouseman, as well as providing CCC with adequate financial data of each warehouseman which already is approved or is applying for a storage contract with CCC.

**Increase the Rate Used in Calculating the Net Worth Requirement of Grain Warehouses from 10 Cents Per Bushel to 20 Cents Per Bushel and Delete the Existing Requirement That a Warehouseman's Net Worth Need Not Exceed $250,000**

There were seven responses to the proposed changes. Three favored the change and four were opposed. The responses were from exporting firms, grain and feed dealer associations, elevator associations, and country elevator operators.

Those in favor of the proposed changes indicated that increasing the net worth requirement from 10 to 20 cents per bushel times the maximum storage capacity and removing the $250,000 net worth ceiling would generally have no overall serious consequences on the grain industry and would provide additional protection to the public. Four respondents opposed the proposal because they believed that increasing the net worth requirement to an unlimited amount from a maximum of $250,000 is a heavy burden for the country warehouseman. They also felt that removing the $250,000 maximum net worth would place an additional cost upon some of the larger firms thereby causing them possible financial difficulties.

A suggested alternative to the proposed rule was that CCC should consider a sliding scale of rates which would be applicable as storage capacity increases rather than providing for a flat rate of 20 cents per bushel regardless of the size of the warehouse. The scale suggested was as follows: for the first one million bushels of capacity, the net worth would be calculated at 20 cents per bushel; for the second one million bushels of capacity, the net worth would be calculated at 15 cents per bushel; and for all storage capacity over two million bushels, the net worth would be calculated at 10 cents per bushel. This alternative was not accepted since it was concluded that it would not provide the desired protection for CCC.

Accordingly, the amendment to the regulation at 7 CFR 1421.5552(a)(3) will be adopted as set forth in the proposed rule.

**Permit the Warehouseman To Furnish CCC an Irrevocable Letter of Credit as Security To Meet the Net Worth Requirements**

There were six responses to the proposed rule. Two favored the change and four were opposed. The responses were from exporting firms, elevator associations, grain and feed dealer associations, elevator operators and banks.

Those in favor of the proposed change stated that an irrevocable letter of credit would provide an acceptable substitute security for a deficiency in net worth. The four respondents opposing the use of an irrevocable letter of credit felt the letter of credit would be impossible to obtain from local banks in smaller towns due to the $100 million dollar asset requirement. After careful consideration of the written and verbal comments, it has been concluded that the regulations at 7 CFR § 1421.5553 should be revised to require only that the irrevocable letter of credit must be issued by a commercial bank insured by the Federal Deposit Insurance Corporation (FDIC). The irrevocable letter of credit provides the warehouseman with another form of acceptable security for a net worth deficiency which may be obtained at a lower cost than the traditional deficiency bond or other substitute security.

**List of Subjects in 7 CFR Part 1421**

Grains, Loan programs—agriculture, Oilseeds, Peanuts, Price support programs, Soybeans, Surety bonds, Tobacco, Warehouses.

**Final Rule**

## PART 1421—GRAINS AND SIMILARLY HANDLED COMMODITIES

Accordingly, the regulations at 7 CFR Part 1421 are amended as follows:

1. In § 1421.5551, paragraph (d)(2) is revised and a new paragraph (e) is added to read as follows:

**§ 1421.5551 General statement and administration.**

* * * * *

(d) * * *

(2) A current financial statement prepared in accordance with generally accepted accounting principles meeting the following requirements:

(i) Each financial statement shall include, but not be limited to the following: (A) A balance sheet; (B) a statement of income (profit and loss); (C) statement of retained earnings; and (D) a statement of changes in the financial position.

(ii) Each financial statement shall be accompanied by one of the following:

(A) A report of audit or review conducted by an independent CPA or an independent public accountant in accordance with standards established by the American Institute of Certified Public Accountants. The accountant's report of audit or review shall include

the accountant's certifications, assurances, opinions, comments, and notes with respect to such financial statement, or

(B) A compilation report of the financial statement which is prepared by a grain commission firm or a management firm if such firm has been authorized by the Deputy Vice President, CCC (Deputy Administrator, Commodity Operations, ASCS) to provide a compilation report of financial statements of warehousemen.

(iii) All financial statements shall be accompanied by a certification by the chief executive officer of the warehouseman, under penalty of perjury, that the financial statement(s) accurately reflects the financial condition of the warehouseman for the period specified in such statement.

(iv) A current Form TW–51, "Financial Statement," containing organizational and general information with the warehouseman's certification shall be submitted with the scheduled financial statements or as the Agricultural Marketing Service (AMS) or CCC may request.

(v) Only one financial statement will be required for a chain of warehouses owned or operated as a single business entity, unless otherwise determined by CCC.

* * * * *

(e) The provisions of paragraph (d)(2) of this section shall also be applicable to warehousemen who have an existing storage contract with CCC. Such warehousemen with existing storage contracts shall submit their financial statements to CCC in the manner prescribed reflecting their financial condition as of the close of the warehouseman's fiscal or calendar year's operation, whichever is applicable. Thereafter, the financial statements and the audit, review or compilation reports shall be furnished annually to reflect the warehouseman's fiscal or calendar year's operation, whichever is applicable, and at such other times as may be required by the AMS or CCC.

* * * * *

2. In § 1421.5552, paragraph (a)(3) is revised to read as follows:

**§ 1421.5552 Basic standards.**

(a) * * *

(3) Have a net worth which is the greater of $25,000 or the amount which results from multiplying the maximum storage capacity of the warehouse (the total quantity of the commodity involved which the warehouse can accommodate when stored in the customary manner) under approved contract with CCC times twenty (20) cents per bushel in the case of grain, forty (40) cents per hundredweight in the case of rough rice, seventy (70) cents per hundredweight in the case of milled rice, and fifty (50) cents per hundredweight in the case of dry edible beans. In the case of seed, the net worth of the warehouseman shall be at least equal to the product obtained by multiplying the estimated total number of pounds of seed to be stored times six (6) cents per pound. If the calculated net worth exceeds $25,000, the warehouseman may satisfy any deficiency in net worth between the $25,000 minimum requirement and such calculated net worth by furnishing bonds, irrevocable letters of credit, or other acceptable substitute security meeting the requirements of § 1421.5553.

* * * * *

3. Section 1421.5553 is amended by adding a new paragraph (e) to read as follows:

**§ 1421.5553 Bonding requirement for net worth.**

* * * * *

(e) An irrevocable letter of credit may be accepted by CCC in lieu of the required amount of bond coverage provided that the issuing bank is a commercial bank insured by the Federal Deposit Insurance Corporation. Such letter of credit shall be on Form CCC–33A, "Irrevocable Letter of Credit."

(Sec. 4 and 5, 62 Stat. 1070, as amended (15 U.S.C. 714b and c))

Signed at Washington, D.C. on May 20, 1982.

**Everett Rank,**

*Executive Vice President, Commodity Credit Corporation.*

[FR Doc. 82–14228 Filed 5–24–82; 8:45 am]

BILLING CODE 3410–05–M

## CIVIL AERONAUTICS BOARD

### 14 CFR Part 384

**[Amdt. No. 17; Reg. OR–197]**

### Transfer of Office Functions

**AGENCY:** Civil Aeronautics Board.

**ACTION:** Final rule.

**SUMMARY:** The CAB revises its statement of organization to reflect a staff reorganization.

**DATES:** Adopted: May 20, 1982. Effective: May 25, 1982.

**FOR FURTHER INFORMATION CONTACT:** Mark Schwimmer, Office of the General Counsel, Civil Aeronautics Board, 1825 Connecticut Avenue, N.W., Washington, D.C. 20428, 202–673–5442.

**SUPPLEMENTARY INFORMATION:** Effective February 1, 1982, the Board combined the functions of its Office of Community and Congressional Relations with the consumer protection functions of its Bureau of Compliance and Consumer Protection (BCCP) in a new Office of Congressional, Community, and Consumer Affairs (OCCCA). The Litigation Division of BCCP, which participated in enforcement cases, was transferred to the Office of the General Counsel and renamed as the Enforcement Division. The Investigation Division of BCCP was transferred to the Bureau of Carrier Accounts and Audits (BCAA).

In OR–190, 47 FR 5204, February 4, 1982, the Board amended its delegations of authority in 14 CFR Part 385 to reflect these changes. The Board is now amending the general statement of organization in 14 CFR Part 384 to reflect the same changes.

Since these amendments are administrative in nature, affecting agency practice and procedure, the Board finds for good cause that notice and public procedure are unnecessary and that the amendments may become effective less than 30 days after publication in the **Federal Register.**

**List of Subjects in 14 CFR Part 384**

Administrative practice and procedure, Archives and records, Authority delegations.

### PART 384—STATEMENT OF ORGANIZATION, DELEGATION OF AUTHORITY, AND AVAILABILITY OF RECORDS AND INFORMATION

Accordingly, the Civil Aeronautics Board amends 14 CFR Part 384, *Statement of Organization, Delegation of Authority, and Availability of Records and Information,* as follows:

1. The authority for Part 384 is:

**Authority:** Secs. 204, 1001, Pub. L. 85–726, as amended, 72 Stat. 743; 788, 49 U.S.C. 1324, 1481.

2. In § 384.7, paragraphs (a)(2) and (e) are revised, paragraph (f) is removed and reserved, and paragraph (i) is revised, to read:

**§ 384.7 Organization and delegation of authority.**

* * * Generally speaking, the Board's staff comprises:

(a) * * *

(2) The Office of Congressional, Community, and Consumer Affairs, which represents the Board in dealing with representatives of state and local communities and civic groups; identifies community interests and develops

recommendations of Board policies and actions relating thereto; maintains liaison between the Board and Congress; insures that the consumer perspective is represented in all matters considered by the Board; operates programs and provides services to inform and educate consumers in their contacts with the air transportation industry; handles consumer complaints and mediates them where possible.

* * * * *

(e) The Bureau of Carrier Accounts and Audits, which is responsible for serving as the principal accounting policy and program advisor to the Board on all substantive and procedural matters related to air carrier audits, internal audits, and industry accounting transactions and systems, and for providing investigative assistance to other CAB bureaus and offices. This Bureau develops and administers the Board's industry accounting systems; conducts industry audits and examinations of air carrier accounts and records; performs technical staff work in analyzing financial reports or documents used in proceedings requiring expertise in accounting or auditing matters; provides advice on accounting and auditing aspects relevant to monitoring compliance with continuing fitness requirements; and conducts investigations of alleged violations of the Act and the Board's regulations to uncover unfair consumer practices and unfair methods of competition. This Bureau also provides internal audit coverage over all funds, property, and other assets for which the Board is responsible, and provides information and advice concerning carrier compliance records and compliance disposition.

(f) [Reserved]

* * * * *

(i) The Office of the General Counsel, which is responsible for advising the Board, its staff, industry representatives, and the public on legal aspects of the Board's regulatory activities; representing the Board in litigated matters; assisting attorneys in other offices and bureaus as required; representing the Board in negotiations and at conferences where legal matters are involved; representing the Board on Government committees and committees of international organizations; and, through the Enforcement Division under the sole supervision of the Deputy General Counsel, promoting observance of the Federal antitrust laws, the economic provisions of the Federal Aviation Act, and the Board's orders, regulations, and other requirements.

* * * * *

By the Civil Aeronautics Board.

Phyllis T. Kaylor,

*Secretary.*

[FR. Doc. 82-14217 Filed 5-24-82; 8:45 am]

BILLING CODE 6320-01-M

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## 14 CFR Part 385

**[Reg. OR-196; Amdt. No. 124]**

## Delegation to the Associate General Counsel, Pricing and Entry

**AGENCY:** Civil Aeronautics Board.

**ACTION:** Final rule.

**SUMMARY:** When the CAB issues a certificate to a new air carrier, it delays the effective date until 5 days after receipt of a safety report from the Federal Aviation Administration. The CAB now delegates to the Associate General Counsel, Pricing and Entry, the authority to review the FAA report, and to advance the effective date or stay it for up to 30 days, as appropriate. This rule delegates that authority with regard to any new carrier, to avoid the need for further individual delegation orders.

**DATES:** Adopted: May 7, 1982. Effective: May 14, 1982.

**FOR FURTHER INFORMATION CONTACT:** Donald H. Horn, Associate General Counsel, Pricing and Entry, Civil Aeronautics Board, 1825 Connecticut Avenue, N.W., Washington, D.C. 20428; 202-673-5205.

**SUPPLEMENTARY INFORMATION:** In *ALPA v. CAB,* 643 F.2d 935 (2d Cir. 1981), the U.S. Court of Appeals indicated that the Board must consider a safety report from the Secretary of Transportation, *i.e.,* the Federal Aviation Administration (FAA), before granting operating authority to any new air carrier. The Board set out procedures for this function in the *Sun Pacific Airlines Fitness Investigation,* Order 81-6-126, June 18, 1981. Under these procedures, when the Board issues a certificate to a new air carrier it delays the effective date until 5 days after it receives from the FAA copies of the carrier's FAA air carrier operating certificate and operations specifications. These detail the type of operation for which the FAA has qualified the applicant. The Board can thus compare these specifications with its own results and, if there is any discrepancy, issue a stay delaying the effectiveness of the applicant's authority.

Because the 5-day delay can be costly to a carrier that has its equipment and personnel on line and ready to operate, the Board has in two cases delegated authority by order to the Associate General Counsel, Pricing and Entry, to advance the effective date upon a satisfactory review of FAA documents (*JetAmerica Fitness Investigation,* Order 81-11-53, November 10, 1981, delegated authority exercised in Order 81-11-91, November 13, 1981; *Westair Jet Fitness Investigation,* Order 82-1-67, January 15, 1982, delegated authority exercised in Order 82-1-89, January 20, 1982). This rule delegates that authority with regard to any new carrier, to avoid the need for further individual delegation orders.

If the FAA report is unsatisfactory, a stay needs to be issued within 5 days to prevent the certificate from becoming effective. This rule also delegates to the Associate General Counsel the authority to issue such a stay, for up to 30 days, to expedite the process.

Since this amendment is administrative in nature, affecting agency practice and procedure, the Board finds for good cause that notice and public procedure are unnecessary and that the amendment may become effective less than 30 days after publication in the **Federal Register.**

**List of Subjects in 14 CFR Part 385**

Administrative practice and procedure, Authority delegations.

## PART 385—DELEGATION AND REVIEW OF ACTION UNDER DELEGATION; NONHEARING MATTERS

Accordingly, the Civil Aeronautics Board amends 14 CFR Part 385, *Delegation and Review of Action Under Delegation; Nonhearing Matters,* as follows:

1. The authority for Part 385 is:

**Authority:** Secs. 102, 204, 401, 402, 403, 407, 416, Pub. L. 85-726, as amended, 72 Stat. 740, 743, 754, 757, 758, 766, 771, 49 U.S.C. 1302, 1324, 1381, 1372, 1373, 1377, 1386; Reorganization Plan No. 3 of 1961, 26 FR 5989.

2. In § 385.21, a new paragraph (g) is added, to read:

### § 385.21 Delegation to Associate General Counsel, Pricing and Entry.

The Board hereby delegates to the Associate General Counsel, Pricing and Entry, the authority to:

* * * * *

(g) Review Federal Aviation Administration reports on the safety of newly certificated air carriers, and

(1) Amend orders issuing certificates to advance the effective dates of the certificate if the review is satisfactory, or

(2) Stay the effectiveness of such orders for up to 30 days if the review is unsatisfactory.

By the Civil Aeronautics Board:

Phyllis T. Kaylor,

*Secretary.*

[FR Doc. 82-14232 Filed 5-24-82; 8:45 am]

BILLING CODE 6320-01-M

## SECURITIES AND EXCHANGE COMMISSION

## 17 CFR Parts 275 and 279

**[Release No. IA-805]**

## Amendments To Investment Adviser Requirements Concerning Disclosure, Application for Registration and Annual Report

**AGENCY:** Securities and Exchange Commission.

**ACTION:** Adoption of amendments to rules and forms; request for comment.

**SUMMARY:** The Commission is amending certain disclosure and reporting requirements applicable to investment advisers under the Investment Advisers Act of 1940. The amendments adopted on a final basis make certain changes, both substantive and technical, in the investment adviser registration, disclosure, and reporting requirements. The effect of the amendments will be to clarify and simplify the investment adviser registration and disclosure requirements. In addition, the Commission is adopting temporary amendments to other reporting requirements which will further simplify such requirements and is inviting public comments on these amendments.

**DATES:** Effective May 25, 1982. Comments on the temporary amendments must be received on or before July 16, 1982.

**ADDRESSES:** Comments should be submitted in triplicate to: George A. Fitzsimmons, Secretary, Securities and Exchange Commission, 500 North Capitol Street, NW., Washington, D.C. 20549. Comment letters should refer to File No. S7-932. All comments received will be available for public inspection and copying in the Commission's public reference room, 1100 L Street, NW., Washington, D.C.

**FOR FURTHER INFORMATION CONTACT:** Arthur E. Dinerman, Esq., Investment Advisers Study Group, Division of Investment Management, Securities and Exchange Commission, Washington, D.C. 20549; (202) 272-2079.

**SUPPLEMENTARY INFORMATION:**

### I. Background and Summary

On July 21, 1981, the Commission issued a release soliciting public comments on proposed amendments to certain disclosure and reporting requirements applicable to investment advisers under the Investment Advisers Act of 1940 (15 U.S.C. 80b-1 et seq.) ("Advisers Act").[1] The proposed amendments involved a number of technical and clarifying changes in the investment adviser disclosure, registration and reporting requirements. In addition, the Commission proposed to delete Item 17 of Part I of Form ADV (17 CFR 279.1), the investment adviser registration form, and related requirements which obliged certain investment advisers to file an unaudited balance sheet with the Commission and to update it annually. The release also proposed a new Item 17 for Part I pertaining to newsletter publishers.

Having considered the comments submitted, the Commission has decided to adopt the proposed amendments in all but three respects. The Commission is also adopting certain conforming amendments to reflect the deletion of Item 17 from Part I of Form ADV. In addition, the Commission is adopting certain temporary amendments relating to Part I of Form ADV and is soliciting public comments on the temporary amendments.

### II. Amendments

The Commission received eleven comment letters in response to its notice of proposed rulemaking. Although several commentators expressed general support for the proposed amendments, the majority criticized some aspect of the proposal.

Seven commentators objected to the proposal to adopt new Item 17 of Part I of Form ADV requiring publishers of periodical publications to disclose annually the number of their subscribers as of the end of their last fiscal year. The principal criticisms of proposed new Item 17 were that such disclosure was unnecessary or would be burdensome, that disclosure would place smaller publishers at a competitive disadvantage, and that the information disclosed could be used by a publisher's competitors to gauge the success of the marketing techniques used by the publisher. Although the Commission questions the extent to which these results would occur, the Commission has reconsidered its need for the information that would be obtained by proposed new Item 17. As discussed in greater detail in Advisers Act Release No. 766, the Commission proposed new Item 17 in order to obtain information which would assist the Commission's staff in deciding which advisers to inspect at a particular time as well as to provide useful additional data about the advisory industry. However, the information is not essential to the inspection program. Therefore, the Commission has determined not to adopt the proposed new item.

There were two comments pertaining to the proposed change in Rule 204-3(d) (17 CFR 275.204-3(d)) which would permit an investment adviser who renders different types of advisory services to omit from its disclosure statement any information (as opposed to only certain specified information as is now the case) required by Part II of Form ADV which is not applicable to the particular client receiving the statement. Two commentators criticized the proposal for failing to set forth standards as to the meaning of the phrase "different types of investment advisory services to different advisory clients" and offered clarifying language.[2] The Commission agrees that the standards set forth in the commentators' suggestion describe circumstances in which use of a tailored disclosure statement generally would be appropriate. The Commission is concerned, however, that the specific standards suggested by the commentators might be read to limit unnecessarily the circumstances under which use of a tailored brochure would be permitted and that it is not feasible to set forth standards which would encompass all circumstances in which use of a tailored brochure would be appropriate. The Commission believes that use of the general phrase contained in the proposal is preferable to the suggested alternative in that it provides registrants maximum flexibility in determining for themselves when they can use a tailored disclosure statement. Therefore, the Commission is adopting

[1] Investment Advisers Act Release No. 766 (46 FR 38529, July 28, 1981).

[2] The Commission proposed to amend rule 204-3(d) to read: Omission of inapplicable information. If an investment adviser renders *substantially different types of investment advisory services to different advisory clients*, any information required by Part II of Form ADV may be omitted from the statement furnished to an advisory client or prospective advisory client if such information is applicable to a type of advisory service or fee which is not rendered or charged, or proposed to be rendered or charged, to that client or prospective client.

The commentators suggested substituting for the underlined language the following: * * * services that differ as among investment advisory clients classified in terms of account size, investment objective, types of permissible investments or nature of accounts involved (e.g., ERISA vs. non-ERISA). * * *

the revision to Rule 204–3(d) as proposed.

The Commission is also not adopting the proposed amendments to Items 15(iii) and 16(iii) of Part I of Form ADV which would have added an additional size category to these questions. As discussed below, the Commission has determined to delete Items 15(iii) and 16(iii) of Part I of Form ADV in their entirety.

In addition, the Commission is adopting conforming amendments to reflect the deletion of old Item 17 from Part I of Form ADV. Specifically, the Commission is amending Instructions 12 and 24 and Schedule G of Form ADV, Instruction 6 and Item 4 of Form ADV–S, and rule 204–1(b)(2) (17 CFR 275.204–1(b)(2)), by deleting reference to Item 17.

### III. Temporary Amendments

The Commission, as part of a comprehensive re-evaluation of the regulatory system applicable to investment advisers,[3] has reviewed the reporting and disclosure requirements applicable to investment advisers, including Form ADV, the investment adviser registration application form. As a result of this review, the Commission has decided to adopt certain temporary amendments to Form ADV which will delete a number of items from Part I of Form ADV. These items are Items 5(b), 7(b), 13(b), 15(i) and 15(iii), and 16(i) and 16(iii).

The Commission has determined that the information contained in the items to be deleted, although generally useful to the Commission in its understanding of the investment advisory industry, may not be sufficiently important to justify continuation of the requirements. Items 15(i) and (iii) and 16(i) and (iii) are being deleted because compliance with these items, which require certain registrants to rank by size of assets under management their ten largest categories of clients and to set forth the number of clients which fall into various size categories, appears to involve substantial effort for many registrants. Collection of this information in the past has enabled the Commission to build a data base useful for developing a profile of the investment advisory industry. However, it now appears that the benefits of continuing to collect the information are insufficient in view of the apparent cost and burden to investment advisers in supplying it.

Item 13(b), which requires the investment adviser to disclose whether or not a substantial part of its business consists of rendering "investment supervisory services" as defined in section 202(a)(13) of the Advisers Act (15 U.S.C. 80b–2(a)(13)), is being deleted because it is somewhat duplicative of Item 1(a) of Part II of Form ADV, which requires the investment adviser to disclose whether it furnishes such services. Item 5(b), which requires disclosure of each class of equity security of the investment adviser, and Item 7(b), which requires the investment adviser to disclose and explain any merger with or acquisition of another registered investment adviser during the previous ten years, have been deleted in order to simplify further Part I of Form ADV, and the utility of this information to the Commission's regulatory program is marginal.

The Commission has determined to adopt these temporary amendments without affording prior notice and opportunity for comment because it finds that prior notice and opportunity for public comment are unnecessary under section 553(b)(B) of the Administrative Procedure Act ("APA") (5 U.S.C. 553(b)(B)). All of these amendments relate to Part I of Form ADV, the part of the form which contains information required by the Commission for its own regulatory purposes. The information which registrants are required to deliver or offer to deliver to clients and prospective clients under Rule 204–3 under the Advisers Act, the "brochure rule," is contained in Part II of Form ADV. Accordingly, none of the changes made by the temporary amendments involve information regularly disclosed by registrants to clients and prospective clients. Since the deletions relieve registrants of the obligation to file certain information with the Commission and do not diminish disclosure to clients, the Commission does not believe that any person will be adversely affected by elimination of these items from Part I of Form ADV and, accordingly, has determined that soliciting public comment prior to adopting such deletions is unnecessary.

Although, as discussed above, the Commission finds that prior notice and opportunity for comment with respect to adoption of the temporary amendments are not required under Section 553(b)(B) of the APA, the Commission nonetheless has determined to adopt the amendments on only a temporary basis and is soliciting public comment as to whether the amendments should be made permanent. The temporary amendments will be effective until March 31, 1983, and, accordingly, will be applicable to all initial registrations and amendments filed prior to that date as well as all fiscal year 1982 Form ADV–S filings.

The Commission has also determined to make the amendments and temporary amendments effective immediately in accordance with section 553(d)(1) of the APA (5 U.S.C. 553(d)(1)). None of the amendments or temporary amendments imposes additional substantive requirements on investment advisers. The amendments and temporary amendments to the investment adviser registration application procedures and forms adopted today involve deletions of information previously required to be filed, simplification of procedures to be followed by investment advisers, or technical changes and clarifications of existing requirements. Accordingly, the Commission finds good cause for making the amendments and temporary amendments adopted today effective immediately, so that they will be applicable, as discussed above, to new registrants as well as current registrants meeting their annual filing requirements during fiscal year 1982.

Although the amendments and temporary amendments adopted herein are effective upon publication in the **Federal Register**, forms revised to reflect these amendments will not be available immediately. Until revised forms become publicly available, investment advisers filing initial registration applications with the Commission and registrants who are amending their investment adviser registration application on Form ADV or filing Form ADV–S should use old Form ADV and ADV–S respectively but need not respond to Items 5(b), 7(b), 13(b), 15(i) and (iii) and 16(i) and (iii) of Part I of Form ADV, or file unaudited balance sheets pursuant to Item 17 of Form ADV. Similarly, registrants should respond to Form ADV–S as if the modifications being made in this release were already reflected in the form.

### Regulatory Flexibility Act

The Chairman of the Commission has certified that the amendments being adopted will not have a significant economic impact on a substantial number of small entities. Accordingly, no regulatory flexibility analysis is required under Section 604 of the Regulatory Flexibility Act (5 U.S.C. 601 et seq.).

### List of Subjects in 17 CFR Parts 275, 279

Investment advisers, Reporting requirements, Securities.

[3] In Securities Act Release No. 6323 (June 24, 1981) (46 FR 33287), the Commission stated that Advisers Act Rules 204–1 and 204–3 (17 CFR 275.204–1 and 275.204–3) would be reviewed in 1981.

## PART 275—RULES AND REGULATIONS, INVESTMENT ADVISERS ACT OF 1940

### Commission Action

I. The Commission hereby amends Part 275 of Chapter II of Title 17 of the Code of Federal Regulations as follows:

1. By adding paragraphs (c) and (d) to § 275.203–1 to read as follows:

**§ 275.203–1 Application for registration of investment adviser.**

* * * * *

(c) A Form ADV filed by an investment adviser corporation which is not registered when such form is filed and which succeeds to and continues the business of a predecessor corporation registered as an investment adviser shall be deemed to be an application for registration even though designated as an amendment if the succession is based solely on a change in the predecessor's state of incorporation and the amendment is filed to reflect that change.

(d) A Form ADV filed by an investment adviser corporation, partnership, sole proprietorship or other entity which is not registered when such form is filed and which succeeds to and continues the business of a predecessor corporation, partnership, sole proprietorship or other entity registered as an investment adviser shall be deemed to be an application for registration even though designated as an amendment if the succession is based solely on a change in the predecessor's form of organization and the amendment is filed to reflect that change.

2. By revising paragraphs (b)(2) and (b)(3) of § 275.204–1 to read as follows:

**§ 275.204–1 Amendments to application for registration.**

* * * * *

(b) * * *

(2) If the information contained in response to questions 5, 7, 8, 9 and 11 of Part I, or any question in Part II (Except question 13), or any application for registration as an investment adviser, or in any amendment thereto, becomes inaccurate but not in a material manner, or the information contained in response to questions 12(c), 13, 15 and 16 of Part I of any application for registration as an investment adviser, or in any amendment thereto, becomes inaccurate for any reason, the investment adviser shall file an amendment on Form ADV (Section 279.1 of this chapter) correcting such information within 90 days of the end of its fiscal year. In addition, a balance sheet, as required by question 13 of Part II, shall be filed within 90 days of the end of applicant's fiscal year.

(3) If the information contained in response to question 3 of Part I becomes inaccurate, the investment adviser shall file an amendment on Form ADV, correcting such information within 90 days of the end of the applicant's fiscal year. However, if the investment adviser's registration or license in another jurisdiction has been restricted, suspended, terminated (either voluntarily or involuntarily) or withdrawn, the investment adviser shall promptly file an amendment.

* * * * *

3. By revising paragraph (d) of § 275.204–3 to read as follows:

**§ 275.204–3 Written disclosure statements.**

* * * * *

(d) *Omission of inapplicable information.* If an investment adviser renders substantially different types of investment advisory services to different advisory clients, any information required by Part II of Form ADV may be omitted from the statement furnished to an advisory client or prospective advisory client if such information is applicable only to a type of investment advisory service or fee which is not rendered or charged, or proposed to be rendered or charged, to that client or prospective client.

* * * * *

## PART 279—FORMS PRESCRIBED UNDER THE INVESTMENT ADVISERS ACT OF 1940

II. The Commission hereby amends Part 279 of Chapter II of Title 17 of the Code of Federal Regulations as follows:

**§ 279.1 [Amended]**

1. By amending Form ADV as follows:

(i) Instruction 12 is amended by deleting the last sentence from the first paragraph thereof and substituting the following:

In addition, a balance sheet, as required by question 13 of Part II shall be filed no later than 90 days after the end of applicant's fiscal year.

Instruction 12 is also amended by deleting the last sentence of the second paragraph thereof and substituting therefor the following:

However, if the investment adviser's license or registration has been restricted, suspended, terminated (either voluntarily or involuntarily), or withdrawn, the investment adviser shall promptly file an amendment.

(ii) Instruction 15 is amended by deleting the word "State" in the first line thereof.

(iii) Instruction 24 is amended by deleting the phrase "Item 17 of Part I and."

(iv) Item 3(b) of Part I is amended by deleting the words "or involuntarily terminated or withdrawn or voluntarily terminated" in the second line thereof and substituting therefor the words, "terminated (either voluntarily or involuntarily), or withdrawn."

(v) Item 10(i) of Part I is amended by deleting the comma between the words "desist" and "and" in the first line thereof.

(vi) Item 17 of Part I is amended by deleting such item in its entirety.

(vii) Items 6(a) and 6(b) of Part II are amended by deleting the word "age" in the first line of Item 6(a) and in the second line of Item 6(b) and substituting therefor the words "year of birth."

(viii) The unnumbered note to item 8(b) of Part II is amended to read in its entirety as follows:

Note.—Pursuant to Section 202(a)(12) of the Act (15 U.S.C. 80b–2(a)(12)), the term "affiliated person" has the same meaning as in Section 2(a)(3) of the Investment Company Act of 1940 (15 U.S.C. 80a–2(a)(3)), which provides that an "affiliated person" of another person means:

(A) any person directly or indirectly owning, controlling, or holding with power to vote, 5 per centum or more of the outstanding voting securities of such other person; (B) any person 5 per centum or more of whose outstanding voting securities are directly or indirectly owned, controlled, or held with power to vote, by such other person; (C) any person directly or indirectly controlling, controlled by, or under common control with, such other person; (D) any officer, director, partner, co-partner, or employee of such other person; (E) if such other person is an investment company, any investment adviser thereof or any member of an advisory board thereof; and (F) if such other person is an unincorporated investment company not having a board of directors, the depositor thereof.

(ix) Item 9(c) of Part II is amended by adding the parenthetical phrase "(investment advisory)" immediately after the word "from" in the second line thereof.

(x) Item 9(d) of Part II is amended by adding the parenthetical phrase "(investment advisory)" immediately after the word "prospective" in the first line thereof.

(xi) Item 13 of Part II is amended by deleting the text of such item in its entirety and substituting therefor the following:

Balance Sheet. Every applicant who has custody or possession of clients' funds or securities, or requires prepayment of advisory fees six months or more in advance and in excess of $500 per client, shall provide on Schedule G a balance sheet as of the end

of applicant's most recent fiscal year. The balance sheet shall be audited by an independent public accountant and shall be prepared in accordance with generally accepted accounting principles. The balance sheet shall be accompanied by a note stating the accounting principles and practices followed in its preparation, the basis at which securities are included and other notes as may be necessary for an understanding of the statement. If securities are included at cost, their market or fair value shall be shown parenthetically. The If securities are included at cost, their market or qualifications and any report of an independent accountant which accompanies a balance sheet shall conform with the requirements of Article 2 of Regulation S–X (17 CFR 210.2–01 et seq.).

A sole proprietor investment adviser must show assets and liabilities related to his advisory business separately from his other business and personal assets and liabilities. However, appropriate aggregation of the other business and personal assets and liabilities is permitted except where a deficiency of assets exists in his overall financial position, in which case full details of the other business and personal assets and liabilities shall be presented on the balance sheet or included in a note referred to on the balance sheet.

Has applicant provided a balance sheet on Schedule G pursuant to this Item? Yes ☐ No ☐

(xii) Schedule D, page 2 is amended by adding a request for the name and social security number of the person for whom the schedule is being completed.

(xiii) Schedule G is amended by deleting the phrase "Item 17 of Part I or" from the description of the form.

(A copy of Form ADV, as amended, has been filed with the Office of the Federal Register as part of the original document.)

**§ 279.3 [Amended]**

2. By amending Form ADV–S as follows:

(i) Instruction 2 is amended by adding after the last sentence thereof the following:

Note.—The filing of Form ADV–S does not relieve a registrant of any requirement of Rule 204–1 under the Act to amend its Form ADV. Failure to amend Form ADV, as required by Rule 204–1, could result in enforcement action by the Commission. Any amendment to registrant's Form ADV, which is made at the time registrant's Form ADV–S is filed, may be filed with the Commission concurrently with the filing of Form ADV–S. However, any amendments to Form ADV so filed should *not* be attached to Form ADV–S and should include a properly completed execution page and page one of Part I of Form ADV.

(ii) Instruction 5 is amended by deleting the second and third sentences thereof and substituting therefor the following:

Any registrant which provides an affirmative answer to Item 3(a) should file the required amendment(s) with the Commission on Form ADV, pursuant to the instructions thereto, and indicate in Item 3(b) whether such amendment(s) have been filed concurrently with the filing of Form ADV–S.

Such instruction is amended further by deleting in its entirety the second note to that instruction.

(iii) Instruction 6 is amended to read as follows:

Item 4 requires a registrant to indicate whether it has filed with the Commission on Schedule G of Form ADV, as an amendment to Form ADV, a balance sheet as of the end of such registrant's most recent fiscal year, if applicable. The balance sheet must meet the requirements of Item 13 of Part II of Form ADV.

(iv) Item 4 is amended by deleting the text of such item in its entirety and substituting therefor the following:

(a) Is the registrant subject to the filing requirements of Item 13 of Part II of Form ADV? (Pursuant to Item 13 of Part II of Form ADV, every applicant who has custody or possession of clients' funds or securities or requires prepayment of advisory fees six months or more in advance and in excess of $500 per client, shall provide on Schedule G a balance sheet as of the end of applicant's most recent fiscal year. The balance sheet shall be audited by an independent public accountant and shall be prepared in accordance with generally accepted accounting principles. The balance sheet shall be accompanied by a note stating the accounting principles and practices followed in its preparation, the basis at which securities are included and other notes as may be necessary for an understanding of the statement. If securities are included at cost, their market or fair value shall be shown parenthetically. The qualifications and any report of an independent accountant which accompanies a balance sheet shall conform with the requirements of Article 2 of Regulation S–X (17 CFR 210.2–01 et seq.)). Yes ☐ No ☐

(b) If the answer to Item 4(a) is yes, has the registrant, pursuant to Rule 204–1(b)(2) and Item 13 of Part II of Form ADV, filed with the Commission on Schedule G of Form ADV, a balance sheet as of the end of registrant's most recent fiscal year? Yes ☐ No ☐

(A copy of Form ADV–S, as amended, has been filed with the Office of the Federal Register as part of the original document.)

III. The Commission hereby temporarily amends, until March 31, 1983, Part 279 of Chapter II of Title 17 of the Code of Federal Regulations as follows:

**§ 279.1 [Suspended in part]**

1. By amending Part I of Form ADV as follows:

* * * * *

(i) Item 5 of Part I is amended by deleting part (b) in its entirety and by deleting the designation "(a)."

(ii) Item 7 of Part I is amended by deleting part (b) in its entirety and by deleting the designation "(a)."

(iii) Item 13 of Part I is amended by deleting part (b) in its entirety and by deleting the designation "(a)."

(iv) Item 15 of Part I is amended by deleting parts (i) and (iii) in their entirety and by deleting the designation "(ii)."

(v) Item 16 of Part I is amended by deleting parts (i) and (iii) in their entirety and by deleting the designation "(ii)."

**Statutory Authority**

The Commission (i) amends Rules 204–1 and 204–3 and Form ADV–S pursuant to the authority contained in sections 204, 206(4) and 211(a) of the Advisers Act (15 U.S.C. 80b–4, 80b–6(4) and 80b–11(a)) and (ii) amends Rule 203–1 Form ADV pursuant to the authority contained in Sections 203 (15 U.S.C. 80b–3), 204, 206(4) and 211(a) of the Act.

**George A. Fitzsimmons**

*Secretary.*

May 14, 1982.

**Regulatory Flexibility Act Certification**

I, John S. R. Shad, Chairman of the Securities and Exchange Commission, hereby certify, pursuant to 5 U.S.C. 605(b), that the amendments and temporary amendments adopted herein to Rules 203–1, 204–1 and 204–3 and Forms ADV and ADV–S under the Investment Advisers Act of 1940 ("Advisers Act") will not have a significant economic impact on a substantial number of small entities. The reasons for this certification are that the amendments will impose no additional burdens on investment advisers subject to registration under the Advisers Act; some of the amendments and temporary amendments adopted herein clarify existing requirements while others eliminate previously existing requirements for certain registrants; and these amendments and temporary amendments will reduce the burden on investment advisers subject to registration in complying with Rules 203–1, 204–1 and 204–3 and Forms ADV and ADV–S under the Advisers Act.

Dated: May 14, 1982.

John S. R. Shad,

*Chairman.*

[FR Doc. 82–14183 Filed 5–24–82; 8:45 am]

BILLING CODE 8010–01–M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 74, 81, and 82**

**[Docket No. 82N-0127]**

## D&C Red No. 30

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is permanently listing D&C Red No. 30 for general use in drugs and cosmetics excluding use in the area of the eye. This rule will remove D&C Red No. 30 from the provisional list of color additives for general use in drugs and cosmetics.

**DATES:** Effective June 25, 1982; objections by June 24, 1982.

**ADDRESS:** Written objections may be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Andrew D. Laumbach, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5690.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of November 20, 1968 (33 FR 17205), FDA announced that a petition (CAP 7C0058) for the permanent listing of D&C Red No. 30 as a color additive for use in ingested drugs, lipsticks, and externally applied drugs and cosmetics had been filed by the Toilet Goods Association, Inc. (now the Cosmetic, Toiletry and Fragrance Association (CTFA)), the Pharmaceutical Manufacturers Association (PMA), and the Certified Color Industry Committee (now the Certified Color Manufacturers Association, Inc. (CCMA)), c/o Hazelton Laboratories, Inc., Post Office Box 30, Falls Church, VA 22046 (now 9200 Leesburg Turnpike, Vienna, VA 22180).

The petition was filed under section 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 376). A later notice (41 FR 9584; March 5, 1976) amended the notice of filing of the petition to include the use of D&C Red No. 30 in all types of cosmetics subject to ingestion and the additional use of D&C Red No. 30 in cosmetics intended for use in the area of the eye.

### Toxicological Concerns

The provisional regulations published in the **Federal Register** of February 4, 1977 (42 FR 6992) required new chronic toxicity studies for D&C Red No. 30 as a condition of its continued provisional listing for ingested uses. FDA placed these requirements on 31 color additives, including D&C Red No. 30, because the toxicity studies the petitioners had submitted to support the safe use of these color additives were deficient in several respects. FDA described these deficiencies in the **Federal Register** of September 23, 1976 (41 FR 41863):

1. Many of the studies were conducted using groups of animals, i.e., control and those fed the color additive, that are too small to permit conclusions to be drawn today on the chronic toxicity or carcinogenic potential of the color. The small number of animals used does not, in and of itself, cause this result, but when considered together with the other deficiencies in this listing, does do so. By and large, the studies used 25 animals in each group; today FDA recommends using at least 50 animals per group.

2. In a number of the studies, the number of animals surviving to a meaningful age was inadequate to permit conclusions to be drawn today on the chronic toxicity or carcinogenic potential of the color additives tested.

3. In a number of the studies, an insufficent number of animals was reviewed histologically.

4. In a number of the studies, an insufficient number of tissues was examined in those animals selected for pathology.

5. In a number of the studies, lesions or tumors detected under gross examination were not examined microscopically.

The closing date for the provisional listing of the color additive was postponed until January 31, 1981, for the completion of required chronic toxicity studies.

### Chemistry Concerns

The provisional regulations of February 4, 1977, also established a closing date of October 31, 1977, for developing chemistry data and analytical methods necessary for defining chemical specifications for certifying batches of D&C Red No. 30. FDA requires chemical specifications based on sufficiently precise analytical methods, so that the agency can certify that batches of each color additive are equivalent to the batches of the color additive used in conducting animal studies to establish the safety of the color additive.

The petitioners had been actively engaged in efforts to provide the chemistry information needed to establish specifications for the color additive since the petition was submitted to the agency. By 1977 it was evident from experimental data that D&C Red No. 30 contained unidentified components for which specifications would have to be considered by the agency. FDA expected that the chemical nature and amount of these unidentified components, which are soluble in acetone, would be resolved during the postponement of the closing date until October 31, 1977. The petitioner notified the agency that work was underway to provide the necessary information in response to the new closing date. FDA expected that the use of new analytical techniques, such as high-pressure liquid chromatography (HPLC), would lead to rapid resolution of the chemistry issues. However, this task proved to be more difficult to complete during the short postponement period than the agency expected. As a result, the petitioners, in a letter dated October 6, 1977, requested a further extension of time to complete the chemistry analysis of D&C Red No. 30. On the basis of chemistry reports showing satisfactory progress in developing the analytical methods necessary to define specifications for D&C Red No. 30, FDA allowed the continued provisional listing for the color additive until January 31, 1981, the same closing date the agency established for completion of the toxicity studies discussed above.

FDA later again extended the closing date for completing the chronic toxicity studies and submitting data. In a proposal in the **Federal Register** of November 14, 1980 (45 FR 75226), the agency outlined the reasons for the need to postpone the closing dates for 23 provisionally listed color additives under test, including D&C Red No. 30, beyond January 31, 1981.

Although the agency had decided to postpone the closing date for D&C Red No. 30 and the other color additives before expiration of the January 31, 1981 closing date, the order did not publish before President Reagan signed his Executive Memorandum of January 29, 1981, which directed Federal agencies to postpone for 60 days all pending regulations, with certain exemptions inapplicable to postponements of closing dates for provisionally listed color additives. As soon as possible after the end of the regulatory postponement, FDA issued, in the **Federal Register** of March 27, 1981 (46 FR 18958), the rule establishing new closing dates for D&C Red No. 30 and the other color additives. Therefore, the current closing date for the provisional listing of the color additive is May 30, 1982.

**Resolution of Toxicological and Chemical Concerns**

The agency has completed its evaluation of the color additive petition for D&C Red No. 30, including two new chronic toxicity studies in rats and mice. These new long-term chronic studies represent current state-of-the-art toxicological testing. The protocols for these studies have benefited from knowledge or deficiencies in previously conducted carcinogenesis bioassays and other chronic toxicity protocols. The use of large numbers of animals of both sexes, pilot studies to determine maximum tolerated dosages, two control groups (thereby effectively doubling the number of controls), and in utero exposure in one of the two species tested significantly increase the power of these tests to detect dose-related effects. The studies were designed and conducted in full compliance with the good laboratory practices regulations and were subject to inspections by FDA officials during their course.

Based on the evaluation of the results of the two new chronic toxicity studies, the agency has determined that D&C Red No. 30 is not carcinogenic to Charles River Sprague-Dawley rats or CD–1 mice after lifetime dietary exposue of 2.0 percent and 5.0 percent, respectively. Using appropriate safety factors (see 21 CFR 70.40), the agency has also estimated a maximum acceptable daily intake for humans—1.25 milligrams per kilogram of body weight per day.

FDA has also evaluated the scientific data regarding the chemical characterization of D&C Red No. 30 and its acetone-soluble components. Modern HPLC analytical methods establish that the acetone-soluble portion of the color additive is a complex mixture consisting of several compounds, each being present in very small amounts. The batch of D&C Red No. 30 fed in the test diets of the animals in the chronic toxicity studies contained approximately 2.8 percent acetone-soluble material. Therefore, the feeding tests also served to test the toxicity of the impurities. These tests provided no evidence that the acetone-soluble material is toxic.

To ensure the safety of future batches of this color additive, however, FDA is establishing a specification limit on the amount of acetone-soluble material that it will permit in D&C Red No. 30. Analysis of batches of this color additive that have been produced in recent years reveals that the acetone-soluble material is typically present in the finished color additive at a level of 2 to 5 percent. The exaggerated doses used in the feeding studies establish the safety of the color additive when the acetone-soluble matter is present at these typical levels. Therefore, FDA is setting the specification at 5 percent for this matter.

To ensure further the safety of the color additive, the agency has determined that it is necessary to control the qualitative and quantitative character of the acetone-soluble fraction. To ensure that the quantity and quality of the acetone-soluble components in individual batches conform to current good manufacturing practice, FDA will analyze by the HPLC method samples of the color additive submitted for certification, and FDA will compare the results of that analysis to those obtained with the sample tested toxicologically. Details of the HPLC method will be provided upon request from the contract person listed above.

**Conclusion on Safety**

The agency concludes that D&C Red No. 30 is safe under conditions of use set forth below for general use in drugs and cosmetics, and that certification is necessary for the protection of the public health. The final toxicity study reports, interim reports, and the agency's toxicology evaluations of these studies are on file at the Dockets Management Branch (address above). They may be reviewed there during working hours, between 9:30 a.m. and 4 p.m.

FDA notified the petitioners by letters, dated May 14, 1976, August 15, 1977, and August 4, 1978, of the need for data to support the use of D&C Red No. 30 in cosmetics intended for use in the area of the eye. In the latest letter, dated October 24, 1978, FDA advised the petitioners to consider withdrawing their petition that sought approval of use of D&C Red No. 30 in cosmetics intended for use in the area of the eye because it appeared that the required data from eye-area studies would not be readily available.

The required data for eye-area use have not been submitted to the agency. Therefore, that portion of the petition that was amended by the filing on March 5, 1976 (Docket No. 76C–0044) to include the permanent listing of D&C Red No. 30 for eye-area use is now considered by the agency to be withdrawn without prejudice in accordance with the provisions of § 71.4 (21 CFR 71.4). Section 71.4 requires that such requested information be submitted within 180 days after filing of the petition, or the petition will be considered withdrawn without prejudice. Use of D&C Red No. 30 in the area of the eye has never been covered by provisional listing. Future consideration by FDA of the permanent listing of D&C Red No. 30 for eye-area use will require the submission of a new color additive petition for that use. The agency's listing of a color additive for general use in drugs and cosmetics does not encompass eye-area use.

The agency has determined under 21 CFR 25.24 (b)(12) and (d)(5) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant effect on the environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

**List of Subjects in 21 CFR Parts 74, 81, 82**

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 706 (b), (c), and (d), 74 Stat. 399–403 (21 U.S.C. 376 (b), (c), and (d))) and the Transitional Provisions of Color Additive Amendments of 1960 (Title II, Pub. L. 86–618, sec. 203, 74 Stat. 404–407 (21 U.S.C. 376, note)); and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1); see 46 FR 26052; May 11, 1981), Parts 74, 81, and 82 are amended as follows:

## PARTS 74—LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

1. Part 74 is amended:

a. By adding new § 74.1330 to Subpart B, to read as follows:

**§ 74.1330 D&C Red No. 30.**

(a) *Identity.* (1) The color additive D&C Red No. 30 is principally 6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[*b*]thien-2(3*H*)-ylidene)-4-methyl-benzo[*b*]thiophen-3(2*H*)-one (CAS Reg. No. 2379–74–0).

(2) Color additive mixtures for drug use made with D&C Red No. 30 may contain only those diluents that are suitable and that are listed in Part 73 of this chapter as safe for use in color additive mixtures for coloring drugs.

(b) *Specifications.* D&C Red No. 30 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice:

Volatile matter (at 135° C), not more than 5 percent.
Chlorides and sulfates (calculated as sodium salts), not more than 3 percent.
Matter soluble in acetone, not more than 5 percent.
Total color, not less than 90 percent.

Lead (as Pb), not more than 20 parts per million.
Arsenic (as As), not more than 3 parts per million.
Mercury (as Hg), not more than 1 part per million.

(c) *Uses and restrictions.* D&C Red No. 30 may be safely used for coloring drugs generally in amounts consistent with current good manufacturing practice.

(d) *Labeling.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(e) *Certification.* All batches of D&C Red No. 30 shall be certified in accordance with regulations in Part 80 of this chapter.

b. By adding new § 74.2330 to Subpart C, to read as follows:

**§ 74.2330 D&C Red No. 30.**

(a) *Identity and specifications.* The color additive D&C Red No. 30 shall conform in identity and specifications to the requirements of § 74.1330 (a)(1) and (b).

(b) *Uses and restrictions.* D&C Red No. 30 may be safely used for coloring cosmetics generally in amounts consistent with current good manufacturing practice.

(c) *Labeling requirements.* The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(d) *Certification.* All batches of D&C Red No. 30 shall be certified in accordance with regulations in Part 80 of this chapter.

## PART 81—GENERAL SPECIFICATIONS AND GENERAL RESTRICTIONS FOR PROVISIONAL COLOR ADDITIVES FOR USE IN FOODS, DRUGS, AND COSMETICS

2. Part 81 is amended:

**§ 81.1 [Amended]**

a. In paragraph (b) of § 81.1 *Provisional lists of color additives* by removing the entry for "D&C Red No. 30."

**§ 81.27 [Amended]**

b. In § 81.27 *Conditions of provisional listing,* by removing the entry for D&C Red No. 30 in the introductory text of paragraph (c) and in paragraphs (c)(1) and (d).

## PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS

3. Part 82 is amended by revising § 82.1330, to read as follows:

**§ 82.1330 D&C Red No. 30.**

The color additive D&C Red No. 30 shall conform in identity and specifications to the requirements of § 74.1330 (a)(1) and (b) of this chapter.

Any person who will be adversely affected by the foregoing regulation may at any time on or before June 24, 1982, file with the Dockets Management Branch (address above) written objections thereto. Objections shall show wherein the person filing will be adversely affected by the regulation, specify with particularity the provisions of the regulation deemed objectionable, and state the grounds for the objections. Objections shall be filed in accordance with the requirements of 21 CFR 71.30. If a hearing is requested, the objections shall state the issues for the hearing and shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Three copies of all documents shall be filed and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

*Effective date.* This regulation shall become effective June 25, 1982, except as to any provisions that may be stayed by the filing of proper objections. Notice of the filing of objections or lack thereof will be announced by publication in the Federal Register.

(Sec. 706 (b), (c), and (d), 74 Stat. 399–403 (21 U.S.C. 376 (b), (c), and (d)); sec. 203, Pub. L. 86–618, 74 Stat. 404–407 (21 U.S.C. 376, note))

Dated: May 18, 1982.

William F. Randolph,

*Acting Associate Commissioner for Regulatory Affairs.*

[FR Doc. 82-14064 Filed 5-24-82; 8:45 am]
BILLING CODE 4160-01-M

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**21 CFR Part 81**

**[Docket No. 76N-0366]**

## Provisional Listing of D&C Red No. 30; Postponement of Closing Date

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is postponing the closing date for the provisional listing of D&C Red No. 30 for general use in drugs and cosmetics excluding use in the area of the eye. A new closing date for D&C Red No. 30 is being established to provide for receipt and evaluation of any objections submitted in response to the final regulation approving the petition for the listing of D&C Red No. 30 for this use. The regulation that lists D&C Red No. 30 is published elsewhere in this issue of the Federal Register. The new closing date will be July 29, 1982.

**EFFECTIVE DATE:** May 28, 1982.

**FOR FURTHER INFORMATION CONTACT:** Andrew D. Laumbach, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–472–5690.

**SUPPLEMENTARY INFORMATION:** The current closing date of May 30, 1982, for the provisional listing of D&C Red No. 30 was established by a rule published in the Federal Register of March 27, 1981 (46 FR 18958). The May 30, 1982 closing date for D&C Red No. 30 was established to provide time for determining the applicability of the statutory standard for the listing of color additives to the results of scientific investigations of D&C Red No. 30.

After reviewing and evaluating the data, the agency has concluded that D&C Red No. 30 is safe for that use. Therefore, elsewhere in this issue of the Federal Register, FDA is publishing a regulation that lists D&C Red No. 30.

The regulation set forth below will postpone the May 30, 1982 closing date for the provisional listing of that color additive until July 29, 1982. This postponement will provide sufficient time for receipt and evaluation of comments or objections submitted in response to the regulation that lists D&C Red No. 30 for general use in drugs and cosmetics, excluding use in the area of the eye.

Because of the shortness of time until the May 30, 1982 closing date, FDA concludes that notice and public procedure on this regulation are impracticable. Moreover, good cause exists for issuing this postponement as a final rule, because the agency has concluded that D&C Red No. 30 is safe for its intended use under the Color Additive Amendments of 1960. This regulation will permit the uninterrupted use of this color additive until July 29, 1982. To prevent any interruption in the provisional listings of D&C Red No. 30, and in accordance with 5 U.S.C. 553(d) (1) and (3), this regulation is being made effective on May 30, 1982.

**List of Subjects in 21 CFR Part 81**

Color additives, Cosmetics, Drugs.

Therefore, under the Transitional Provisions of the Color Amendments of 1960 to the Federal Food, Drug, and

Cosmetic Act (Title II, Pub. L. 86-618, sec. 203, 74 Stat. 404-407 (21 U.S.C. 376 note)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), Part 81 is amended in § 81.1 *Provisional list of color additives,* by revising the closing date for "D&C Red No. 30" in paragraph (b) to read "July 29, 1982."

*Effective date.* This regulation is effective May 28, 1982.

(Sec. 203, 74 Stat. 404-407 (21 U.S.C. 376 note))

Dated: May 18, 1982.

**William F. Randolph,**

*Acting Associate Commissioner for Regulatory Affairs.*

[FR Doc. 82-14070 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## 21 CFR Part 175

**[Docket No. 81F-0309]**

## Indirect Food Additives: Adhesive Coatings and Components; Polyamide Coatings for Polypropylene Film

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of polyamide resins derived from dimerized vegetable oil or tall oil acids, azelaic acid, ethylenediamine, and piperazine as the basic resin in coatings for polypropylene film in contact with food. This action is being taken in response to a petition filed by Union Camp Corp., Chemical Division.

**DATE:** Effective May 25, 1982.

**ADDRESS:** Written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Patricia J. McLaughlin, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5690.

**SUPPLEMENTARY INFORMATION:** In a notice published in the **Federal Register** of November 10, 1981 (46 FR 55564), FDA announced that a petition (FAP 8B3384) had been filed by Union Camp Corp., Chemical Division, P.O. Box 2668, Savannah, GA 31402, proposing that the food additive regulations be amended to provide for the safe use of polyamide resins derived from dimerized vegetable oil acids, azelaic acid, ethylenediamine, and piperazine as the basic resin in coatings for polypropylene film in contact with food. Dimerized tall oil acids are included.

FDA has evaluated the data in the petition and other relevant material and concludes that the proposed food additive use is safe and that § 175.320 (21 CFR 175.320) should be amended as set forth below. In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Bureau of Foods (address above) by appointment with the information contact person listed above. As provided in § 171.1(h)(2), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

### List of Subjects in 21 CFR Part 175

Adhesives, Food additives, Food packaging.

## PART 175—INDIRECT FOOD ADDITIVES: ADHESIVE COATINGS AND COMPONENTS

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), Part 175 is amended in § 175.320(b)(3)(i) by alphabetically inserting a new item in the list of substances to read as follows:

**§ 175.320 Resinous and polymeric coatings for polyolefin films.**

* * * * *

(b) * * *

(3) * * *

(i) * * *

| List of substances | Limitations |
|---|---|
| * * * * * | |
| Polyamide resins (CAS Reg. No. 68139-70-8), as the basic resin, derived from: | For use only in coatings for polypropylene films that contact food at temperatures not to exceed room temperature. |
| Dimerized vegetable oil or tall oil acids containing not more than 20 percent of monomer acids. | |
| Azelaic acid (CAS Reg. No. 123-99-9) in an amount not to exceed 3.7 percent by weight of the polyamide resin. | |
| Ethylenediamine (CAS Reg. No. 107-15-3). | |
| Piperazine (CAS Reg. No. 110-85-0) in an amount not to exceed 6.4 percent by weight of the polyamide resin. | |
| * * * * * | |

* * * * *

Any person who will be adversely affected by the foregoing regulation may at any time on or before June 24, 1982 submit to the Dockets Management Branch (address above) written objections thereto and may make a written request for a public hearing on the stated objections. Each objection shall be separately numbered and each numbered objection shall specify with particularity the provision of the regulation to which objection is made. Each numbered objection on which a hearing is requested shall specifically so state; failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held; failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this regulation. Received objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

*Effective date.* This regulation shall become effective May 25, 1982.

(Secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348))

Dated: April 20, 1982.

**William F. Randolph,**

*Acting Associate Commissioner for Regulatory Affairs*

[FR Doc. 82-14065 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## 21 CFR Part 178

**[Docket No. 81F-0170]**

## Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers; Antioxidants and or Stabilizers for Polymers

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of 2,2'-ethylidenebis(4,6-di-*tert*-butylphenol) as an antioxidant and/or stabilizer in certain polymers in contact with food. This action is being taken in response to a petition filed by Schenectady Chemicals, Inc.

**DATES:** Effective May 25, 1982; objections by June 24, 1982.

**ADDRESS:** Written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Patricia J. McLaughlin, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5690.

**SUPPLEMENTARY INFORMATION:** In a notice published in the **Federal Register** of June 30, 1981 (46 FR 33637), FDA announced that a petition (FAP 1B3559) had been filed by Schenectady Chemicals, Inc., P.O. Box 1046, Schenectady, NY 12301, proposing that § 178.2010 (21 CFR 178.2010) be amended to provide for the safe use of 2,2'-ethylidenebis(4,6-di-*tert*-butylphenol) as an antioxidant and/or stabilizer for polymers in contact with food.

FDA has evaluated the data in the petition and other relevant material and concludes that the proposed food additive use is safe and that the regulations should be amended as set forth below. In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Bureau of Foods (address above) by appointment with the information contact person listed above. As provided in § 171.1(h)(2), the agency will remove from the documents any materials that are not available for public disclosure before making the documents available for inspection.

The agency has considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding may be seen in the Dockets Management Branch (address above), between 9 a.m. and 4 p.m., Monday through Friday.

**List of Subjects in 21 CFR Part 178**

Food additives, Food packaging Sanitizing solutions.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), Part 178 is amended in § 178.2010(b) by alphabetically inserting a new item in the list of substances to read as follows:

## PART 178—INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS

**§ 178.2010 Antioxidants and/or stabilizers for polymers.**

* * * * *

(b) * * *

| Substances | Limitations |
|---|---|
| * * * * * * * | |
| 2,2'-Ethylidenebis(4,6-di-*tert*-butylphenol) (CAS Reg. No. 35958-30-6). | For use only:<br>1. At levels not to exceed 0.1 percent by weight of olefin polymers complying with § 177.1520(c) of this chapter, item 1.1, 1.2, 1.3, 3.1, or 3.2 (where the polymers complying with items 3.1 and 3.2 contain primarily polymer units derived from propylene).<br>2. At levels not to exceed 0.05 percent by weight of olefin polymers complying with § 177.1520(c) of this chapter, item 2.1, 2.2, or 2.3. The finished polymers are to be used only under conditions of use B through H described in table 2 of § 176.170(c) of this chapter.<br>3. At levels not to exceed 0.075 percent by weight of olefin polymers complying with § 177.1520(c) of this chapter, item 2.1, 2.2, or 2.3 (where the density of each of these polymers is not less than 0.94 g/cc) and item 3.1 or 3.2 (where each of these polymers contains primarily polymer units derived from ethylene).<br>4. At levels not to exceed 0.05 percent by weight of olefin polymers complying with § 177.1520(c) of this chapter, item 3.3, 3.4, 3.5, or 4.<br>5. At levels not to exceed 0.1 percent by weight of ethylene vinyl acetate copolymers complying with § 177.1350 of this chapter and under conditions of use C through G described in table 2 of § 176.170(c) of this chapter.<br>6. At levels not to exceed 0.1 percent by weight of rigid or semirigid polyvinyl chloride and under conditions of use B through H described in table 2 of § 176.170(c) of this chapter. |
| * * * * * * * | |

Any person who will be adversely affected by the foregoing regulation may at any time on or before June 24, 1982 submit to the Dockets Management Branch (address above), written objections thereto and may make a written request for a public hearing on the stated objections. Each objection shall be separately numbered and each numbered objection shall specify with particularity the provision of the regulation to which objection is made. Each numbered objection on which a hearing is requested shall specifically so state; failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held; failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this regulation. Received objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

*Effective date.* This regulation shall become effective May 25, 1982.

(Secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348))

Dated: May 18, 1982.

**William F. Randolph,**

*Acting Associate Commissioner for Regulatory Affairs.*

[FR Doc. 82-14068 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## 21 CFR Parts 436, 440, 442, 444, and 446

**[Docket No. 82N-0136]**

## Antibiotic Drugs; Updating and Technical Changes

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the antibiotic regulations by updating and by making noncontroversial technical changes in the regulations providing for the certification of certain antibiotic and antibiotic-containing drugs for human use. These changes will result in more accurate and usable regulations that reflect current certification practices.

**DATES:** Effective May 25, 1982; comments, notice of participation, and request for hearing by June 24, 1982; data, information, and analyses to justify a hearing by July 26, 1982.

**ADDRESS:** Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Joan Eckert, Bureau of Drugs (HFD-140), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4290.

**SUPPLEMENTARY INFORMATION:** FDA is amending the antibiotic drug regulations by updating and by making minor noncontroversial technical changes in several antibiotic drug regulations that provide for certification of antibiotic and antibiotic-containing drugs intended for human use. To aid in understanding the types of changes included in this document, the changes have been grouped into two general classes for discussion in this preamble: updating and technical changes.

### Updating

1. In § 436.102, paragraphs (b) (18) and (b) (20) through (29) are removed and reserved. These paragraphs contain descriptions of media that are no longer used in any test methods currently performed in FDA's laboratories.

2. In § 436.103(a), the table is amended as follows:

a. Test organisms M, N, P, Q, R, S, and U are removed. These test organisms are no longer used in any test methods currently performed in FDA's laboratories.

b. Medium 28 listed in the second and third columns for test organism V is replaced with medium 1. Medium 1 is actually used in preparing this test organism.

c. The words oleandomycin and triacetyloleandomycin are removed from footnote"1". This dilution factor is no longer used for these antibiotic drugs.

3. In § 436.103, paragraph (b)(4) is removed and reserved. This paragraph describes a method for a preparation of a suspension of a test organism that is no longer being used in any test methods performed in FDA's laboratories.

4. In § 436.105 (a) and (b), the items chloramphenicol, cycloserine, griseofulvin, and troleandomycin are removed from the tables, wherever they appear. The test method under this section is no longer used for these drugs.

5. In § 436.106(b), a "Note" is added immediately before the table to provide for testing smaller volumes of material in the microbacterial turbidimetric assay.

6. In § 446.542(b)(2)(ii), the last sentence is revised to prevent injection of the entire filtrate of a meclocycline sample solution into the chromatograph.

### Technical Changes

1. In § 436.105(b), footnote "7" is added at the end of the table and a superior figure reference "7" is added to "Not dried" in the second column of the table for the item sisomicin. Because of the loss of potency of sisomicin on drying, it is necessary to take two portions of the standard to complete the assay. One portion is used for the determination of moisture and the other portion is used for the determination of potency.

2. In § 440.241(a)(1), the pH range for nafcillin sodium monohydrate for injection (5.0 to 8.0) is revised to read 6.0 to 8.5. The quality of the product has improved resulting in a higher pH.

3. In § 442.104b(a)(1), the upper pH limit for cefaclor monohydrate for oral suspension is raised from 4.5 to 5.0. The sole manufacturer has submitted adequate stability data to support the higher limit.

4. In § 444.342b(b)(1)(ii), the use of thioglycolic acid is removed from the polymyxin potency assay for neomycin sulfate-polymyxin B sulfate-gramicidin ophthalmic solution. FDA's laboratory, the National center for Antibiotics Analysis, has determined that it is not necessary for the accuracy of the assay.

The agency has determined pursuant to 21 CFR 25.24(b)(22) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

### List of Subjects in 21 CFR

*Part 436*

Antibiotics.

*Part 440*

Antibiotics, penicillin.

*Part 442*

Antibiotics, cepha.

*Part 444*

Antibiotics, oligosaccharide.

*Part 446*

Antibiotics, tetracycline.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 507,701 (f) and (g), 52 Stat. 1055-1056 as amended, 59 Stat. 463 as amended (21 U.S.C. 357, 371 (f) and (g))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), Parts 436, 440, 442, 444, and 446 are amended as follows:

## PART 436—TESTS AND METHODS OF ASSAY OF ANTIBIOTIC AND ANTIBIOTIC-CONTAINING DRUGS

1. Part 436 is amended as follows:

**§ 436.102 [Amended]**

a. In § 436.103 *Culture media* by removing and reserving paragraph (b) (18), (20), (21), (22), (23), (24), (25), (26), (27), (28), and (29).

**§ 436.103 [Amended]**

b. In § 436.103 *Test organisms,* the table in paragraph (a) is amended by removing test organisms M, N, P, Q, R, S, and U, by changing "28" to "1" in the second and third columns for test organism V, by removing "oleandomycin," and "or triacetyloleandomycin," from footnote "1", and by removing and reserving paragraph (b)(4).

c. In § 436.105, the table in paragraph (a) is amended by removing the items "chloramphenicol," "cycloserine," "griseofulvin," and "troleandomycin," the table in paragraph (b) is amended by removing the items "chloramphenicol," "cycloserine," and "griseofulvin," and by revising the item "sisomicin," to read as follows:

**§ 436.105 Microbiological agar diffusion assay.**

* * * * *

(b) * * *

| Antibiotic | Working standard stock solutions | | | | | Standard response line concentrations | |
|---|---|---|---|---|---|---|---|
| | Drying conditions (method number as listed in § 436.200) | Initial solvent | Diluent (solution number as listed in § 436.101(a)) | Final concentration units or milligrams per milliliter (milligrams) | Storage time under refrigeration (days) | Diluent | Final concentrations, units or micrograms of antibiotic activity per milliliter |
| • | • | • | • | • | • | • | • |
| Sisomicin [6] | Not dried [7] | | 3 | 1 | 14 | 3 | 0.064, 0.080, 0.100, 0.125, and 0.156 grams. |
| • | • | • | • | • | • | • | • |

[6] Working standard should be stored below minus 20° C under an atmosphere of nitrogen. Sisomicin is hygroscopic and care should be exercised during weighing.
[7] Weigh a separate portion of the working standard and determine the loss on drying by the method described in § 436.200(c) of this chapter. Use this value to determine the anhydrous content of the working standard.

**§ 436.106 [Amended]**

d. In § 436.106 *Microbiological turbidimetric assay,* paragraph (b) is amended by adding the following **Note** immediately before the table:

**Note.**—The amount of working standard and sample solutions may be reduced as long as all other solutions used are reduced proportionately.

## PART 440—PENICILLIN ANTIBIOTIC DRUGS

2. Part 440 is amended in § 440.241(a)(1) by revising the seventh sentence, to read as follows:

**§ 440.214 Nafcillin sodium monohydrate for injection.**

(a) * * *

(1) * * * When reconstituted as directed in the labeling, the pH is not less than 6.0 and not more than 8.5. * * *

* * * * * *

## PART 442—CEPHA ANTIBIOTIC DRUGS

3. Part 442 is amended in § 442.104b(a)(1) by revising the fifth sentence, to read as follows:

**§ 442.104b Cefaclor monohydrate for oral suspension.**

(a) * * *

(1) * * * When reconstituted as directed in the labeling, its pH is not less than 2.5 and not more than 5.0. * * *

* * * * * *

## PART 444—OLIGOSACCHARIDE ANTIBIOTIC DRUGS

**§ 444.342b [Amended]**

4. Part 444 is amended in § 444.342b *Neomycin sulfate-polymyxin B sulfate-gramicidin ophthalmic solution* in paragraph (b)(1)(ii) by removing the third sentence.

## PART 446—TETRACYCLINE ANTIBIOTIC DRUGS

5. Part 446 is amended in § 446.542(b)(2)(ii) by revising the last sentence, to read as follows:

**§ 446.542 Meclocycline sulfosalicylate cream.**

* * * * * *

(b) * * *

(2) * * *

(ii) * * * Inject the filtrate onto the column as described in § 436.329(e) of this chapter.

* * * * * *

These amendments institute changes that are corrective, editorial, or of a minor substantive nature. Because the amendments are not controversial and because when effective they provide notice of accepted standards, FDA finds that notice, public procedure, and delayed effective date are unnecessary and not in the public interest. The amendments, therefore, are effective May 25, 1982. However, interested persons may, on or before June 24, 1982, submit written comments on this regulation to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Any person who will be adversely affected by this regulation may file objections to it and request a hearing. Reasonable grounds for the hearing must be shown. Any person who decides to seek a hearing must file (1) on or before June 24, 1982, a written notice of participation and request for hearing, and (2) on or before July 26, 1982, the data, information, and analyses on which the person relies to justify a hearing, as specified in 21 CFR 430.20. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that no genuine and substantial issue of fact precludes the action taken by this order, or if a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who request(s) the hearing, making findings and conclusions and denying a hearing. All submissions must be filed in three copies, identified with the docket number appearing in the heading of this order, and filed with the Dockets Management Branch.

The procedures and requirements governing this order, a notice of participation and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and grant or denial of a hearing are contained in 21 CFR 430.20.

All submissions under this order, except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the Dockets Management Branch, between 9 a.m. and 4 p.m., Monday through Friday.

Effective date: This regulation shall be effective May 25, 1982.

(Secs. 507, 701 (f) and (g), 52 Stat. 1055–1056 as amended, 59 Stat. 463 as amended (21 U.S.C. 357, 371 (f) and (g)))

Dated: May 18, 1982.

**James C. Morrison,**

*Acting Assistant Director for Regulatory Affairs.*

[FR Doc. 82-14140 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

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**21 CFR Part 520**

## Oral Dosage Form New Animal Drugs not Subject to Certification; Diethylcarbamazine Citrate Chewable Tablets

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a new animal drug application (NADA) filed by Beecham Laboratories, providing for safe and effective use of diethylcarbamazine citrate chewable tablets for prevention of heartworm disease and as an aid in

the treatment of ascarid infections in dogs.

**EFFECTIVE DATE:** May 25, 1982.

**FOR FURTHER INFORMATION CONTACT:** Bob G. Griffith, Bureau of Veterinary Medicine (HFV-112), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3430.

**SUPPLEMENTARY INFORMATION:** Beecham Laboratories, Division of Beecham, Inc., Bristol, TN 37620, filed NADA 128-517 providing for use of 60-, 120-, and 180-milligram (mg) diethylcarbamazine citrate chewable tablets for prevention of heartworm disease in dogs caused by *Dirofilaria immitis,* and as an aid in the treatment of ascarid *(Toxocara canis,* and *Toxascaris leonina)* infections in dogs.

The product is similar to another tablet that was the subject of a National Academy of Sciences/National Research Council (NAS/NRC) review which was published in the **Federal Register** of January 8, 1969 (34 FR 275). The NAS/NRC review stated, and the agency concurred, that diethylcarbamazine is probably not effective as a treatment against filariasis, that more information is needed regarding the dosage level to support claims for prevention of filariasis, and that the drug is effective as an aid in the treatment of ascarid infections in dogs and cats when administered at 25 to 50 mg per pound of body weight as a single dose with a repeat dose given after 10 to 20 days. Sponsors of NADA's for products which did not reflect the conclusions of the notice were required to update their applications by submitting revised labeling or adequate documentation to support the labeling used. Those sponsors whose NADA's satisfied the requirements of the NAS/NRC notice or were found equivalent to the NAS/NRC reviewed products are codified in the regulations in 21 CFR 520.620 and 520.622.

A NAS/NRC review of another dosage form, diethylcarbamazine medicated premix, was published in the **Federal Register** of June 16, 1970 (35 FR 9869). The review concluded that the product is probably effective, and the agency concluded that it is effective, as an aid in the prevention and elimination of large roundworms (ascarids) in dogs when given as directed. The review established the effectiveness of the drug for use in prevention of ascarid infections.

Beecham Laboratories submitted data from a controlled artificial challenge study, a palatability study, and reprints from published scientific literature to demonstrate that diethylcarbamazine is safe and effective for use, as labeled, in prevention of heartworm disease. The agency granted a waiver from the requirements of 21 CFR 514.111(a)(5)(ii) for further studies to provide substantial evidence of effectiveness for that claim. The claims for control and treatment of ascarid infections are approved on the basis of the NAS/NRC reviews. The NADA is approved and the regulations are amended to reflect the approval.

In accordance with the freedom of information provisions of Part 20 (21 CFR Part 20) and § 514.11(e)(2)(ii) (21 CFR 514.11(e)(2)(ii)), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, from 9 a.m. to 4 p.m., Monday through Friday.

The Bureau of Veterinary Medicine has determined pursuant to 21 CFR 25.24(d)(1)(i) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This action is governed by the provisions of 5 U.S.C. 556 and 557 and is therefore excluded from Executive Order 12291 by section 1(a)(1) of the Order.

**List of Subjects in 21 CFR Part 520**

Animal drugs, oral use.

## PART 520—ORAL DOSAGE FORM NEW ANIMAL DRUGS NOT SUBJECT TO CERTIFICATION

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(i), 82 Stat. 347 (21 U.S.C. 360(i))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)) and redelegated to the Bureau of Veterinary Medicine (21 CFR Part 5.83), Part 520 is amended in § 520.622c by adding new paragraph (b)(7) to read as follows:

**§ 520.622c Diethylcarbamazine citrate chewable tablets.**

* * * * *

(b) * * *

(7) For 000029 use of 60-, 120-, or 180-milligram tablets as in paragraph (c)(2)(ii) of this section.

* * * * *

*Effective date:* May 25, 1982.

(Sec. 512(i), 82 Stat. 347 (21 U.S.C. 360b(i)))

Dated: May 18, 1982.

Gerald B. Guest,

*Acting Director, Bureau of Veterinary Medicine.*

[FR Doc. 82-14068 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

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**21 CFR Part 520**

## Oral Dosage Form New Animal Drugs not Subject to Certification; Levamisole Hydrochloride Paste

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration is amending the animal drug regulations to reflect approval of a new animal drug application (NADA) filed for Cyanamid Agricultural de Puerto Rico, Inc., providing for safe and effective use of levamisole hydrochloride paste in cattle for treating nematode infections.

**EFFECTIVE DATE:** May 25, 1980.

**FOR FURTHER INFORMATION CONTACT:** William D. Price, Bureau of Veterinary Medicine (HFV-123), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3442.

**SUPPLEMENTARY INFORMATION:** Cyanamid Agricultural de Puerto Rico, Inc. (CAPRI), Manati, PR 00701, is the sponsor of an NADA (126-237) filed on its behalf by American Cyanamid Co. The application provides for use of levamisole hydrochloride paste in cattle for treating infections of stomach worms, intestinal worms, and lung worms. Approval is based on data contained in NADA's 39-356, 39-357, and 44-015 and on well-controlled studies with this new oral dosage form. The NADA is approved, and the regulations are amended to provide for use of the new dosage form.

Under the Bureau of Veterinary Medicine's supplemental approval policy of (42 FR 64367; December 23, 1977), approval of this NADA has been treated as would the approval of a Category II supplement and did not require reevaluation of the safety and effectiveness data in related NADA's 39-356, 39-357, and 44-015.

The Bureau of Veterinary Medicine has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The Bureau's finding of no significant impact and the evidence supporting this finding, contained in a statement of exemption (pursuant to 21

CFR 25.1 (f)(1)(iii)), may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with the freedom of information provisions of Part 20 (21 CFR Part 20) and § 514.11(e)(2)(ii) (21 CFR 514.11(e)(2)(ii)), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (address above), from 9 a.m. to 4 p.m., Monday through Friday.

This action is governed by the provisions of 5 U.S.C. 556 and 557 and is therefore excluded from Executive Order 12291 by section 1(a)(1) of the Order.

**List of Subjects in 21 CFR Part 520**

Animal drugs, oral use.

## PART 520—ORAL DOSAGE FORM NEW ANIMAL DRUGS NOT SUBJECT TO CERTIFICATION

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(i), 82 Stat. 347 (21 U.S.C. 360b(i))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)) and redelegated to the Bureau of Veterinary Medicine (21 CFR 5.83), Part 520 is amended by adding new § 520.1242f to read as follows:

**§ 520.1242f Levamisole hydrochloride paste.**

(a) *Specifications.* The drug is a paste containing 11.5 percent levamisole hydrochloride.

(b) *Sponsor.* See No. 043781 in § 510.600(c) of this chapter.

(c) *Related tolerances.* See § 556.350 of this chapter.

(d) *Conditions of use.* It is used in cattle as follows:

(1) *Amount.* Eight milligrams of levamisole hydrochloride per kilogram of body weight, as a single oral dose.

(2) *Indications for use.* Anthelmintic effective against the following nematode infections: Stomach worms (*Haemonchus, Trichostrongylus, Ostertagia*), intestinal worms (*Trichostrongylus, Cooperia, Nematodirus, Bunostomum, Oesophagostomum*), and lungworms (*Dictyocaulus*).

(3) *Limitations.* Conditions of constant helminth exposure may require re-treatment within 2 to 4 weeks after the first treatment; do not administer to dairy cattle within 6 days of slaughter for food; do not administer to animals of breeding age; consult veterinarian before using in severely debilitated animals.

Effective date. May 25, 1982.

(Sec. 512(i), 82 Stat. 347 (21 U.S.C. 360b(i)))

Dated: May 18, 1982.

**Gerald B. Guest,**

*Acting Director, Bureau of Veterinary Medicine.*

[FR Doc. 82-14066 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

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**21 CFR Part 558**

## New Animal Drugs for Use in Animal Feeds; Tylosin and Sulfamethazine

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a new animal drug application (NADA) sponsored by Old Monroe Elevator & Supply Co., Inc., providing for use of a tylosin and sulfamethazine premix to make complete swine feeds.

**EFFECTIVE DATE:** May 25, 1982.

**FOR FURTHER INFORMATION CONTACT:** Jack C. Taylor, Bureau of Veterinary Medicine (HFV-136), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5247.

**SUPPLEMENTARY INFORMATION:** Old Monroe Elevator & Supply Co., Inc., Old Monroe, MO 63369, is sponsor of NADA 128-835 for Thrifty Swine Mix Tylan 5 Sulfa Premix, a premix containing 5 grams per pound each of tylosin (as tylosin phosphate) and sulfamethazine. This NADA provides for safe and effective use of the premix for subsequent manufacture of complete swine feed to be used for (1) maintaining weight gain and feed efficiency in the presence of atrophic rhinitis, (2) lowering the incidence and severity of *Bordetella bronchiseptica*, (3) prevention of swine dysentery (vibronic), and (4) control of swine pneumonias caused by bacterial pathogens (*Pasteurella multocida* and/or *Corynebacterium pyogenes*).

Approval of the application is based on safety and effectiveness data contained in Elanco's approved NADA's 12-491 and 41-275. Elanco has authorized FDA to refer to these applications to support approval of the application. Because this approval does not change the approved use of the drug, it poses no increased human risk from exposure to drug residues and does not affect the conditions of safe use in the target animal species. Accordingly, under the Bureau of Veterinary Medicine's supplemental approval policy (42 FR 64367; December 23, 1977), approval of this NADA has been treated as would approval of a Category II supplement and does not require reevaluation of the safety and effectiveness data in NADA 12-491 and NADA 41-275.

In accordance with the freedom of information provisions of Part 20 (21 CFR Part 20) and § 514.11(e)(2)(ii) (21 CFR 514.11(e)(2)(ii)), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, from 9 a.m. to 4 p.m., Monday through Friday.

The Bureau of Veterinary Medicine has determined pursuant to 21 CFR 25.24(d)(1)(i) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This action is governed by the provisions of 5 U.S.C. 556 and 557 and is therefore excluded from Executive Order 12291 by section 1(a)(1) of the Order.

**List of Subjects in 21 CFR Part 558**

Animal drugs, Animal feeds.

## PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(i), 82 Stat. 347 (21 U.S.C. 360(i))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981) and redelegated to the Bureau of Veterinary Medicine (21 CFR 5.83), Part 558 is amended in § 558.630 *Tylosin and sulfamethazine* by adding, in numerical sequence, drug sponsor code "026948" to paragraph (b)(9).

*Effective date.* May 25, 1982.

(Sec. 512(i), 82 Stat. 347 (21 U.S.C. 360b(i)))

Dated: May 18, 1982.

**Gerald B. Guest,**

*Acting Director, Bureau of Veterinary Medicine.*

[FR Doc 82-14067 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

**21 CFR Part 610**

**[Docket No. 81N-0133]**

## General Biological Products Standards; Amendment of Container Label Requirements

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the biologics regulations to reflect the requirement that the statement: "Caution: Federal law prohibits dispensing without prescription" be placed on labels of all prescription biologicals. The agency is issuing the final rule to clarify an existing licensing requirement that has been enforced for many years.

**EFFECTIVE DATE:** June 24, 1982.

**FOR FURTHER INFORMATION CONTACT:** Joseph Wilczek, Bureau of Biologics (HFB-620), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

**SUPPLEMENTARY INFORMATION:** In the Federal Register of August 7, 1981 (46 FR 40212), FDA published a proposal to amend §§ 610.60 and 610.61 (21 CFR 610.60 and 610.61) to reflect the existing requirement that the statement: "Caution: Federal law prohibits dispensing without prescription" be placed on the labels of all prescription biological products. Interested persons were given until October 6, 1981 to submit written comments regarding the proposal.

Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)(4)) states that a prescription drug is misbranded unless this cautionary statement appears on its label. Section 201.100(b)(1) (21 CFR 201.100(b)(1)) currently requires this cautionary statement for all prescription drugs, including biological products intended for human use. The requirement is being added to the biologics regulations to make clear that it applies to biological products as well as other drugs.

Four comments were received on the proposal. A summary of the comments and FDA's response to the comments follows:

1. One comment from a biologic manufacturer stated that FDA has approved its labels which do not include the word "Caution", but merely the words "Federal law prohibits dispensing without prescription."

The agency acknowledges that it has inadvertently approved these labels. Because the final rule constitutes a labeling change for the manufacturer that could result in some economic hardship, the agency will permit use of the current supply of labels, providing that the next printing of labels will include the word "Caution". This action will preclude any economic hardship to the manufacturer.

2. One comment suggested that the regulation include the words "for prescription biologicals" rather than "if appropriate" after the cautionary statement. The proposed regulation required that the container and package label contain "[t]he statement 'Caution: Federal law prohibits dispensing without prescription,' if appropriate." The comment stated that the phrase "if appropriate" after the cautionary statement is vague and needs clarification.

The agency agrees with the comment and is amending the final rule by deleting the words "if appropriate" and substituting the words "for prescription biologicals".

3. One comment objected to the requirement that the cautionary statement be placed on the container label because of space limitations on small container labels.

The agency is aware that the container label for certain products is too small to contain the cautionary statement and therefore permits that statement to be deleted from such container labels provided that the package label for the product contains the cautionary statement. See § 610.60(c).

4. One comment stated that publication of the proposal was unnecessary, that the proposal should be retracted, and that the document should be published instead as a notice. The comment stated that the proposal is already a statutory requirement in the existing drug regulations because biologicals are considered drugs and therefore are subject to the provisions of the Federal Food, Drug, and Cosmetic Act. The comment further stated that the proposal would merely add volume to an overcrowded Code of Federal Regulations (CFR) without adding substance to it.

It is not the agency's policy to duplicate routinely regulations in the CFR. The agency advises that the proposal was published as a result of industry inquiries on the subject. Large corporations with a legal staff to interpret government regulations are well aware of the statutory basis for the regulation. The agency, however, also is aware that there are many small businesses that cannot afford a legal staff and may not have ready access to a comprehensive set of CFR's for drugs and biologics. For these reasons, the agency is amending the biologics regulations by adding the cautionary statement in the labeling provisions, obviating the need to cross-reference drug regulations. Consequently, the agency rejects the comment.

Accordingly, FDA is adopting the proposal with the one revision as described above.

FDA has reexamined the regulatory impact and regulatory flexibility implications of the final rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act. The final rule is merely a clarification of an existing licensing requirement that has been enforced for many years. The agency believes that the final rule will not affect manufacturers of biological products. Therefore, the agency concludes that the final rule does not warrant designation as a major rule under section 1(b) of Executive Order 12291. For the same reasons, the agency certifies that a regulatory flexibility analysis is not required because the final rule will not have a significant economic impact on a substantial number or small entities.

**List of Subjects in 21 CFR Part 610**

Biologics, labeling.

## PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Therefore, under the Federal Food, Drug, and Comestic Act (secs. 201, 502, 701, 52 Stat. 1040-1042 as amended, 1050-1051 as amended, 1055-1056 as amended (21 U.S.C. 321, 352, 371)) and the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), Part 610 is amended as follows:

1. In § 610.60 by adding new paragraph (a)(6), to read as follows:

**§ 610.60 Container label.**

(a) * * *

(6) The statement: "Caution: Federal law prohibits dispensing without prescription," for prescription biologicals.

* * * * *

2. In § 610.61 by adding new paragraph (t), to read as follows:

**§ 610.61 Package label.**

* * * * *

(t) The statement: "Caution: Federal law prohibits dispensing without prescription," for prescription biologicals.

*Effective date.* June 24, 1982.

(Secs. 201, 502, 701, 52 Stat. 1040–1042 as amended, 1050–1051 as amended, 1055–1056 as amended (21 U.S.C. 321, 352, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262))

Dated May 3, 1982.

**Joseph P. Hile,**

*Associate Commissioner for Regulatory Affairs.*

[FR Doc. 82-14142 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## 21 CFR Part 660

**[Docket No. 81N-0119]**

## Additional Standards for Blood Grouping Serum; Use of Chemically Modified Antisera

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the biologics regulations by revising potency requirements for Blood Grouping Sera to permit marketing of chemically modified Blood Grouping Sera. Current potency test requirements are unsuitable for chemically modified Blood Grouping Sera. The agency is amending the regulations to permit, where appropriate, the use of alternative manufacturing methods, procedures, or potency tests for such products as chemically modified Blood Grouping Sera.

**EFFECTIVE DATE:** June 24, 1982.

**FOR FURTHER INFORMATION CONTACT:** Joseph Wilczek, Bureau of Biologics (HFB–620), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301–443–1306.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of July 7, 1981 (46 FR 35122), FDA published a proposal to amend § 660.25 (21 CFR 660.25) of the biologics regulations to permit alternative manufacturing procedures or test methods in the manufacture of chemically modified Blood Grouping Sera. Manufacturers have developed this new class of products which does not react serologically like traditional Blood Grouping Sera. Serial dilutions of the chemically modified Blood Grouping Sera do not provide satisfactory titer values in direct agglutination assays as prescribed in § 660.25(a)(5). Manufacturers, however, have developed other test methods to ensure the effectiveness of chemically modified Blood Grouping Sera.

The proposed rule stated that alternative test methods or manufacturing procedures would be acceptable to the agency if these methods or procedures provided assurances of the specificity, potency, and effectiveness of the modified Blood Grouping Serum equal to or exceeding the assurances provided by the manufacturing procedures or test methods currently prescribed by the additional standards.

Interested persons were given until September 8, 1981 to submit written comments regarding the proposal. Three comments were received. Two comments fully endorsed the proposed rule. A third comment stated that the proposed rule was not in full compliance with the Regulatory Flexibility Act. That comment was from the Chief Counsel for Advocacy of the U.S. Small Business Administration.

The Small Business Administration's Office of Advocacy is responsible for coordinating implementation of the Regulatory Flexibility Act. The comment stated that there was not enough information presented in the proposal to determine whether the proposed action would have a neutral or beneficial effect on small businesses.

The agency advises that the proposal was a direct result of an industry request to market chemically modified Blood Grouping Sera. There are 11 licensed manufacturers of Blood Grouping Sera, not all of which are small businesses. The agency concludes that the final rule will not affect a substantial number of small entities. Moreover, the final rule places no significant economic burden on manufacturers. On the contrary, the rule is expected to be beneficial to these manufacturers because it will permit them to produce a more effective, safer, and more marketable product. As it simply gives a manufacturer greater flexibility in the techniques used to produce and test the product, the rule's economic impact is not expected to vary depending on the size of the manufacturer. Under its provisions, any manufacturer may elect to produce the new, chemically modified Blood Grouping Sera or the traditional Blood Grouping Sera. The only alternative to the rule would be to apply current potency test requirements to chemically modified Blood Grouping Serum. That approach would prevent manufacturers from marketing this new product because they would not have substitute test methods for evaluating it. Accordingly, the agency is issuing the final rule as proposed, and believes that this action will have a beneficial impact on manufacturers marketing Blood Grouping Sera.

In light of its reexamination of the economic impact of this final rule, FDA has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12291, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354). The decision whether to produce chemically modified Blood Grouping Sera or traditional Blood Grouping Sera remains with the manufacturer and is not imposed on industry by the final rule. The final rule will relieve a restriction on a specific segment of the biologics industry and is expected to result in the availability of a more effective, safer, and more marketable product. Therefore, the agency concludes that the final rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the implementation of the final rule will not have a significant impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

### List of Subjects in 21 CFR Part 660

Biologics, labeling.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), Part 660 is amended in § 660.25 by adding new paragraph (d) to read as follows:

## PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

### § 660.25 Potency test without reference preparations.

* * * * *

(d) *Equivalent methods.* Modification of any particular manufacturing method or procedure, including modification of required potency test procedures, shall be permitted whenever a manufacturer presents evidence demonstrating that the alternative methods, procedures, or tests will provide assurances of the specificity, potency, and effectiveness of the modified Blood Grouping Serum that are equal to or greater than the assurances provided by the methods, procedures, or tests currently prescribed by such standards, and the Director, Bureau of Biologics, so finds and makes such finding a matter of official record.

*Effective date.* This regulation is effective June 24, 1982.

(Sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262))

Dated: May 3, 1982.

Joseph P. Hile,

*Associate Commissioner for Regulatory Affairs.*

[FR Doc. 82-14141 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

### Office of Secretary, Low Income Housing

### 24 CFR Part 888

**[Docket No. R-82-922]**

### Sec. 8 Housing Assistance Payments Program—Financing Adjustment for Fair Market Rents

**AGENCY:** Office of Assistant Secretary for Housing-Federal Housing Commissioner.

**ACTION:** Interim rule.

**SUMMARY:** This interim rule amends the financing adjustment rules for calculating Fair Market Rents to (1) increase the ceiling on interest rates from 12 percent to 14 percent, (2) extend the deadline for start of construction from June 1, 1982 to August 1, 1982, (3) permit use of the financing adjustment in connection with property disposition projects sold by HUD and (4) permit projects funded in fiscal year 1982 to use the financing adjustment. Due to current economic conditions, many project proposals to HUD have been found to be financially infeasible without use of the procedures provided in this rule.

**EFFECTIVE DATES:** Upon expiration of the first period of 30 calendar days of continuous session of Congress after publication, subject to waiver. Further notice of the effective date of this interim rule will be published in the **Federal Register.**

**COMMENT DUE DATE:** Written comments and suggestions will be accepted until June 9, 1982.

**ADDRESS:** Rules Docket Clerk, Office of General Counsel, Room 5218, Department of Housing and Urban Development, 451 7th Street, S.W., Washington, D.C. 20410.

**FOR FURTHER INFORMATION CONTACT:** Steve Silvert, Acting Director, Office of State Agency and Bond Financed Programs, 451 7th Street, S.W., Washington, D.C. 20410, (202) 426-7113. This is not a toll-free number.

**SUPPLEMENTARY INFORMATION:** An interim rule implementing a financing adjustment to FY 1981 Section 8 New Construction and Substantial Rehabilitation Fair Market Rents was published at 46 FR 51903, on October 23, 1981, as an amendment to 24 CFR 888.101(b) and a Note to the 1981 FMRs.

Market rates for Section 8 housing bonds have increased markedly since October 1981, when the interim rule was adopted. As a result, few projects have been able to close using the financing adjustment. The Department has surveyed the pipeline of eligible projects and determined that most such projects cannot be made feasible without amendment of the outstanding rules.

The outstanding rules limit the financing adjustment to that required for a permanent debt service factor corresponding to an interest rate of 12 percent. Interest rates have been consistently above 12 percent since October 1, 1981 and at a level that makes it prohibitively costly for owners of Section 8 projects to pay the discount necessary to bring the effective rate down to 12 percent. The outstanding rules also require developers to post an escrow to reduce the mortgage after completion of the project.

The Department has decided that the ceiling on the permanent debt service factor must be increased if these projects are to be completed. The ceiling on the permanent debt service, which limits Section 8 Fair Market Rents and contract rents, is being increased from that corresponding to an interest rate of 12 percent to that corresponding to an interest rate of 14 percent. At any rate of 14½ percent or less, the owner will be required to pay a discount that reduces the interest cost ½ of one percent. Discounts required to be paid by an owner will thus be predictable and at a level that owners can afford. Present escrow requirement will not be changed. Additional interest costs resulting from a rate in excess of 14½ percent will be borne by the owner.

The deadline date for construction starts of June 1, 1981 imposed by the outstanding rules will be changed so that owners may obtain the benefits of the amended rule. Adjustment of Section 8 funding policies to budgetary constraints has delayed processing of some of these projects. The Department is acting to expedite these actions. A change in the deadline date from June 1, 1982 to August 1, 1982 is necessary if processing of these projects is to be successfully completed.

The Department also is seeking to reduce its inventory of HUD-owned projects and to return these projects to private ownership. It has been decided to make the financing adjustment procedure available to projects sold and substantially rehabilitated under 24 CFR Part 886 to facilitate sales where increased contract rents are necessary in view of current financing costs.

Problems associated with high financing costs also have made it infeasible for owners to proceed with projects funded in fiscal year 1982. Where an owner agrees to have the project processed using fiscal year 1981 FMRs, the amended rule permits use of the financing adjustment procedures.

The Department has determined that this amendment to the procedures for use of a financing adjustment in calculating Fair Market Rents is urgently needed if owners and State and local finance agencies are to successfully process Section 8 projects within very tight deadlines. There are now pending before the Department a number of highly desirable project proposals in which there has been a substantial investment of private and public funds. Due to current economic conditions, these project proposals have been found to be financially infeasible without use of the procedures provided in this rule.

Based on these considerations, the Secretary has determined that this amendment is urgently needed and should become effective as soon as possible. Thus, good cause exists for making this amendment effective less than 30 days after its publication in the **Federal Register.** However, the Secretary is providing 15 days for submission of public comments on this amendment prior to its effective date. If, as a result of comment, the Secretary determines that a change in the standards described in this interim rule is appropriate, either the effective date of the rule will be deferred or the rule will be withdrawn. In addition, all relevant comments and suggestions will be considered in the development of a final rule on this subject.

Section 7(o)(3) of the Department of HUD Act (42 U.S.C. 3535(o)(3)) provides for a delay in effectiveness of this interim rule for a period of 30 calendar days of continuous session of Congress after publication, unless waived by the Chairman and Ranking Minority Members of the Senate Committee on Banking, Housing and Urban Affairs, and the House Committee on Banking, Finance and Urban Affairs. The Secretary has requested such waivers so that the rule can become effective as soon as practicable after completion of the 15-day comment period referred to above. At the time of publication of this interim rule, it is not known whether or when such waivers will be granted. Accordingly, a further notice of the effective date of this interim rule will be published in the **Federal Register.**

A Finding of No Significant Impact with respect to the environment has been made in accordance with HUD regulations in 24 CFR Part 50, which implement Section 102(2)(C) of the National Environmental Policy Act of 1969. The finding is available for public inspection during regular business hours in the Office of the Rules Docket Clerk, Room 5218, 451 Seventh Street, SW., Washington, D.C. 20410.

This rule does not constitute a "major rule" as that term is defined in Section 1(b) of Executive Order 12291 on Federal Regulation issued by the President on February 17, 1981. Analysis of the rule indicates that it does not: (1) Have an annual effect on the economy of $100 million or more; (2) cause a major increase in costs or prices for consumers, individual industries, Federal, state or local government agencies, or geographic regions; or (3) have a significant adverse effect on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

This rule was not listed in the Department's Semi-annual Agenda of Regulations published on August 17, 1981 (46 FR 41708) pursuant to Executive Order 12291 and the Regulatory Flexibility Act.

The Catalogue of Federal Domestic Assistance Program number and title are 14.156, Lower-Income Housing Assistance Program (Section 8).

Pursuant to 5 U.S.C. 605(b) (the Regulatory Flexibility Act), the Undersigned hereby certifies that this rule does not have a significant economic impact on a substantial number of small entities.

**List of Subjects in 24 CFR Part 888**

Rent subsidies.

## PART 888—SECTION 8 HOUSING ASSISTANCE PAYMENTS PROGRAM—FAIR MARKET RENTS AND CONTRACT RENT AUTOMATIC ANNUAL ADJUSTMENT FACTORS

Accordingly, the Note to Schedule A to 24 CFR Part 888 previously published and effective November 9, 1981, is amended as follows:

1. Paragraph A is revised to read as follows:

**A. Establishment of Fair Market Rents by Financing Type**

1. The rents published in Schedule A establishing the fiscal year 1981 Fair Market Rents, including the 5 percent adjustment for projects designed for the elderly (base level FMRs), may be increased by use of a financing adjustment to establish Fair Market Rents reflecting the actual costs of permanent financing of the Section 8 programs for New Construction and Substantial Rehabilitation and in connection with the sale and substantial rehabilitation of HUD-owned projects. This Note provides the method for establishing Fair Market Rents for all financing types, other than loans secured by mortgages purchased under the Government National Mortgage Association Tandem Program for Section 8 projects, and direct loans under Section 202 of the Housing Act of 1959 and Section 515 of the Housing Act of 1949. These financing types are excluded since current fixed interest rates for these programs are low enough to permit the development of feasible projects within the 1981 Fair Market Rents without a financing adjustment.

2. FMRs for 1981 will be determined by adjusting for the difference between (1) rents based on estimated development and operating costs using an assumed debt service factor corresponding to an interest rate of not less than 8 percent and (2) rents based on the same costs using the debt service factor of the actual permanent financing. The actual permanent financing debt service factor may not exceed that corresponding to an interest rate which is the lesser of: (i) 14 percent or (ii) the interest cost of the obligations less ½ percent. The limit will not be applied to reduce the actual permanent debt service factor below that corresponding to an interest rate of 12 percent. Where an Agreement to Enter into Housing Assistance Payment Contract has been executed for a project prior to April 15, 1982, it may not be amended to increase contract rents pursuant to this regulation. To promote cost containment, the procedure for calculating the amount of the financing adjustment shall be based on the exact increase in contract rents necessary to meet a specified increase in debt service needed to cover actual interest costs. This procedure is used to assure that the increase permitted shall be available only to cover financing costs.

3. Base level contract rents shall be determined for the project based on an assumed debt service factor corresponding to an interest rate of not less than 8 percent. These base level contract rents plus any utility allowances shall meet the Fair Market Rent limitations of the base level FMRs and the rent reasonableness limitations. The financing adjustment stated in paragraph C shall then be applied to these base level contract rents to determine the actual contract rents. The resulting contract rents shall be no higher than necessary to cover the actual dollar amount of the debt service required by the actual permanent financing.

2. Paragraph B is amended by revising subparagraphs 1 through 4 to read as follows:

**B. Project Eligibility**

1. To obtain the benefits of the financing adjustment for Fair Market Rents, the owner (and the State Agency approved under Part 883 where it finances the projects) must submit a written request to HUD, dated after the effective date of the Note and before July 14, 1982. The request shall state that the project will be processed in accordance with this Note.

2. The project must be assisted under 24 CFR Part 880, 881, 883, or 886 and be subject to fiscal year 1981 FMRs and current HUD regulations. Projects funded in fiscal year 1982 may use the financing adjustment provided that the owner agrees that all processing shall be in accordance with the fiscal year 1981 FMRs. Projects reprocessed under this procedure after publication of the 1982 FMRs shall continue to be entitled to use the 1981 FMRs and cannot use the 1982 FMRs. All dwelling units must be Section 8 contract units.

3. The Agreement to Enter Into HAP Contract (Agreement) shall include an approved construction schedule and a provision requiring that actual construction shall commence on or before August 1, 1982 and will thereafter continue as set forth in the Agreement.

4. General or limited distribution mortgagors will be required to establish an escrow, funded with cash or by letter of credit, in an amount equal to the difference between the assumed debt service factor and the actual permanent debt service factor (but not greater than that corresponding to a 12 percent interest rate), multiplied by replacement cost for new construction or by the equivalent of replacement cost for substantial rehabilitation. * * *

* * * * *

3. Paragraph C is amended by revising subparagraph 2 to read as follows:

**C. Financing Adjustment**

* * * * *

2. The owner and the financing agency shall certify the actual annual debt service factor of the permanent financing. The actual annual debt service factor may not exceed the applicable limit under Paragraph A above. For projects financed by State Agencies, override (as defined in § 883.302 and including any servicing fee), which must be included in the above interest rate ceiling, shall not exceed 50 basis points. There shall be no financing cost contingency (as defined in § 883.302 and described in § 883.308(e)).

* * * * *

(Sec. 7(d), Department of HUD Act (42 U.S.C. 3535(d)))

Dated: May 3, 1982.

**Philip Abrams,**

*General Deputy Assistant Secretary for Housing-Deputy Federal Housing Commissioner.*

[FR Doc. 82-14193 Filed 5-24-82; 8:45 am]

BILLING CODE 4210-27-M

**DEPARTMENT OF THE TREASURY**

**Bureau of Alcohol, Tobacco and Firearms**

**27 CFR Parts 211 and 213**

**[T.D. ATF-103, Ref: Notice No. 389]**

## Distribution and Use of Denatured Alcohol and Rum and Distribution and Use of Tax-Free Alcohol

**AGENCY:** Bureau of Alcohol, Tobacco and Firearms, Department of the Treasury.

**ACTION:** Final rule, Treasury decision.

**SUMMARY:** This final rule amends regulations in 27 CFR Parts 211 and 213 relating to the requirement for certain dealers and users of denatured spirits and users of tax-free alcohol to make annual application for and receive a withdrawal permit. Under this final rule, these dealers and users would no longer be required to annually reapply for and receive a withdrawal permit. All valid withdrawal permits issued on ATF Forms 1450 (5150.13), 1477 (5150.15), and 1485 (5150.12) will no longer expire on the applicable expiration dates and will continue in effect following the expiration date. New withdrawal permits will not contain an expiration date.

**EFFECTIVE DATE:** May 25, 1982.

**FOR FURTHER INFORMATION CONTACT:** Norman P. Blake or John A. Linthicum, Research and Regulations Branch, Bureau of Alcohol, Tobacco and Firearms, Washington, DC 20226 (202-566-7626).

**SUPPLEMENTARY INFORMATION:**

### I. Background

On October 23, 1981, ATF published a notice of proposed rulemaking, No. 389, in the Federal Register (46 FR 51929). This notice proposed to recodify 27 CFR Parts 211 and 213 into 27 CFR Parts 20 and 22, respectively. In addition, the notice proposed several modernizing and liberalizing changes and the elimination of many administrative and recordkeeping burdens. One specific proposal was the elimination of the requirement for certain permittees to annually make application for and receive a withdrawal permit. All but one of the comments submitted fully supported the notice and encouraged ATF to expeditiously implement the proposed changes.

Under the provisions of Parts 211 and 213, permittees dealing in or using specially denatured spirits and using tax-free alcohol are required to (1) initially make application for and obtain an industrial use permit, (2) initially make application for and obtain a withdrawal permit, and (3) annually renew the withdrawal permit, except that "limited users" are issued a continuing withdrawal permit. The duration of withdrawal permits issued under Part 211 is the 12 month period from November 1 through October 31, and withdrawal permits issued under Part 213 are issued for the period from May 1 through April 30.

ATF has determined that the requirement for annual renewal of withdrawal permits is unnecessary, and in an effort to reduce administrative burdens on both affected permittees and the Government, this document deletes the requirement for more than 6,300 permittees to annually renew their withdrawal permits issued on Forms 1450 (5150.13), 1477 (5150.15), and 1485 (5150.12), and allows, on a continuing basis, the withdrawal of tax-free alcohol or specially denatured spirits after the expiration date on the form. Elimination of this requirement is consistent with the Departments policy of reducing administrative burdens and paperwork.

While this final rule only addresses the elimination of the requirement to annually renew withdrawal permits, ATF is developing further significant rulemaking changes, based on notice of proposed rulemaking, No. 389, and comments received from the public in response to it.

### II. Amendments to Part 211

Part 211 of 27 CFR is amended by:

(a) Removing §§ 211.133 and 211.163, Application for and Renewal of Withdrawal Permit, Form 1477 (5150.15) and 1485 (5150.12), respectively. All valid withdrawal permits for dealers and users of denatured spirits with an expiration date of October 31, 1982 will continue in effect after the expiration date.

(b) Making editorial and conforming changes to §§ 211.22, 211.131, 211.132, 211.161, and 211.162 to reflect the change in duration or renewal of the affected withdrawal permits.

### III. Amendments to Part 213

Part 213 of 27 CFR is amended by:

(a) Removing § 213.111, Application for and Renewal of Withdrawal Permit, Form 1450 (5150.13). All valid withdrawal permits for users of tax-free alcohol with an expiration date of April 30, 1983 will continue in effect after the expiration date.

(b) Making editorial and conforming changes to §§ 213.22, 213.109, 213.110 and 213.173 to reflect the change in duration or renewal of the withdrawal permits on Form 1450 (5150.13).

### Executive Order 12291

It has been determined that this final regulation is not a "major rule" within the meaning of Executive Order 12291, published February 17, 1981, in the Federal Register, because it will not have an annual effect on the economy of $100 million or more; it will not result in a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; and, it will not have significant adverse effects on competition, employment, investment, productivity, innovation, or the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. Further, this final regulation is liberalizing in nature and will aid in reducing industry costs, with subsequent benefits to the consumer.

### Regulatory Flexibility Act

The provisions of the Regulatory Flexibility Act relating to a final regulatory flexibility analysis (5 U.S.C. 604) are not applicable to this final rule because it will not have a significant impact on a substantial number of small entities. This final rule will not have significant secondary or incidental effects on a substantial number of small entities or impose, or otherwise cause, a significant increase in the reporting, recordkeeping, or other compliance burdens on a substantial number of small entities.

This final rule relieves reporting burdens on a substantial number of small entities which is consistent with the intent of the Act.

Accordingly, it is hereby certified under the provisions of section 3 of the Regulatory Flexibility Act (5 U.S.C. 605(b)), that this final rule will not have a significant economic impact and, in fact, relieves recordkeeping and reporting burdens on a substantial number of small entities.

### List of Subjects

*27 CFR Part 211*

Administrative practice and procedures, Advertising, Alcohol and alcoholic beverages, Authority delegations, Chemicals, Claims, Cosmetics, Excise taxes, Labeling, Packaging and containers, Reporting requirements, Surety bonds, Transportation.

*27 CFR Part 213*

Administrative practice and procedures, alcohol and alcoholic beverages, authority delegations, claims,

excise taxes, reporting requirements, surety bonds.

**Drafting Information**

The principal authors of this document are Norman P. Blake and John A. Linthicum, Research and Regulations Branch, Bureau of Alcohol, Tobacco and Firearms.

**Effective Date**

Because the Department has determined that continued adherence to the annual renewal requirement is unnecessary and in order to immediately relieve both affected permittees and the Government from the requirements of filing and processing these documents it is impracticable and not in the public interest to issue this Treasury decision subject to the 30-day effective date limitation in 5 U.S.C. 553(d). Therefore, this Treasury decision is effective on its date of publication in the **Federal Register.**

**Authority and Issuance**

This regulation is issued under the authority of 26 U.S.C. 7805 (68A Stat. 917, as amended). Based on the foregoing, Title 27 CFR is amended as follows:

## PART 211—DISTRIBUTION AND USE OF DENATURED ALCOHOL AND RUM

**Paragraph 1.** The table of sections for Part 211 is amended to reflect (a) the amended heading of § 211.161, and (b) the removal of §§ 211.133 and 211.163. As amended, the table of sections reads as follows:

Sec.

* * * * *

211.133 [Reserved]

* * * * *

211.161 Application for withdrawal permit and limitations on withdrawals.

211.163 [Reserved]

* * * * *

**§ 211.22 [Amended]**

**Par. 2.** Section 211.22 is amended by deleting the words "or renewal" from the undesignated paragraph which follows paragraph (a)(3).

**§ 211.131 [Amended]**

**Par. 3.** Section 211.131 is amended by deleting (a) the words "during the term of the permit" from the second sentence, and (b) the word "annual" from the third sentence.

**Par. 4.** Section 211.132 is revised to read as follows:

**§ 211.132 Issuance and duration of withdrawal permits.**

If the application submitted in accordance with § 211.131 is approved, the regional regulatory administrator shall issue the withdrawal permit on Form 1477 (5150.15) and forward the original to the bonded dealer. Withdrawal permits on Form 1477 (5150.15) shall have the same duration as industrial use permits in accordance with § 211.46.

**§ 211.133 [Removed]**

**Par. 5.** Section 211.133 is removed.

**Par. 6.** Section 211.161 is revised to read as follows:

**§ 211.161 Application for withdrawal permit and limitations on withdrawals.**

(a) *Application.* A user who desires to obtain specially denatured spirits shall, unless application is filed on Form 4326 (5150.21) as provided in § 211.42a, file an application on Form 1485 (5150.12) with the regional regulatory administrator. The user shall specify in the application:

(1) The formula numbers of the denatured spirits to be withdrawn, listing only those formulas covered by Form 1479–A (5150.19) and formulas which will be used exclusively for laboratory or mechanical purposes as provided in § 211.169.

(2) The estimated average quantity, in gallons of denatured spirits of each formula that will be required in 1 month. The applicant shall specify the quantities and the formulas in accordance with business needs. A user may file applications for more than one withdrawal permit and have withdrawals divided among the permits.

(b) *Limitations on withdrawals.* A user holding a permit on Form 1485 (5150.12) may, during any month and as to each formula specified, withdraw not more than twice the number of gallons specified under paragraph (a)(2) of this section, or 55 gallons (one drum), whichever is larger. Regarding any one formula, the total quantity withdrawn annually may not exceed the number of gallons specified under paragraph (a)(2) of this section for 1 month multiplied by 12 in a calendar year. Withdrawals are futher subject to the following limitations:

(1) A user holding a withdrawal permit on Form 1485 (5150.12) authorizing withdrawals of not more than 120 gallons during a 12-month period, without bond, may not withdraw at one time a quantity which would result in there being more than 12 gallons on hand, in transit, and unaccounted for.

(2) A user (other than a State or political subdivision thereof, or the District of Columbia) holding a withdrawal permit on Form 4327 (5150.11) may not withdraw at one time a quantity which would result in there being more than 7 gallons on hand, in transit, and unaccounted for.

(3) A user who has filed bond, and a State, political subdivision thereof, or the District of Columbia, may not withdraw at one time a quantity which would result in there being on hand, in transit, and unaccounted for a quantity exceeding that stated in the application for permit under § 211.43 and § 211.43a, as applicable.

(c) *Exceptions to limitations.* (1) A user whose business is seasonal in nature, or who has other valid reasons, may request in the application for a withdrawal permit, a larger withdrawal of one or more formulas during a specific calendar month or months. The user may also request that the larger withdrawals be allowed on the basis of an aggregate quantity of two or more formulas combined; if so, the user's request shall be specific as to the amounts desired and the formulas involved.

(2) The user shall furnish sufficient information with the application to enable the regional regulatory administrator to evaluate the request for larger withdrawals.

(3) The limitations in paragraph (b) of this section on total withdrawals during the calendar year and on the quantity which may be on hand, in transit, and unaccounted for at any one time, apply to users granted larger withdrawals under this paragraph.

(Sec. 201, Pub. L. 85–859, 72 Stat. 1370, as amended (26 U.S.C. 5271))

**Par. 7.** Section 211.162 is revised to read as follows:

**§ 211.162 Issuance and duration of withdrawal permits.**

If the application submitted in accordance with § 211.161 is approved, the regional regulatory administrator shall issue the withdrawal permit on Form 1485 (5150.12) and forward the original to the permittee. If the application submitted in accordance with § 211.42a is approved, the regional regulatory administrator shall issue the limited withdrawal permit on Form 4327 (5150.11) and forward the original to the permittee. Withdrawal permits on Forms 1485 (5150.12) and 4327 (5150.11) shall have the same duration as industrial use permits in accordance with § 211.46.

**§ 211.163 [Removed]**

**Par. 8.** Section 211.163 is removed.

**§ 211.166 [Amended]**

**Par. 9.** Section 211.166 is amended by revising the last sentence to read as follows: "When space for making entries on withdrawal permit forms is no longer

available, separate sheets, as needed, shall be attached to and made part of the form, and entries covering each shipment shall be made on them in the same manner as on the form."

## PART 213—DISTRIBUTION AND USE OF TAX FREE ALCOHOL

**Par. 10.** The table of sections for Part 213 is amended to reflect (a) the amended heading of § 213.109, and (b) the removal of § 213.111. As amended, the table of sections reads as follows:

Sec.

* * * * *

213.109 Application for withdrawal permit and limitations on withdrawals.

* * * * *

213.111 [Reserved]

* * * * *

### § 213.22 [Amended]

**Par. 11.** Section 213.22 is amended by deleting the words "or renewal" from the undesignated paragraph which follows paragraph (a)(3).

**Par. 12.** Section 213.109 is revised to read as follows:

### § 213.109 Application for withdrawal permit and limitations on withdrawals.

(a) *Application.* A user who desires to obtain tax-free alcohol shall, unless application is filed on Form 4326 (5150.21) as provided in § 213.41a, file an application on Form 1450 (5150.13) with the regional regulatory administrator. The user shall specify in the application the estimated average quantity, in proof gallons of tax-free alcohol that will be required in 1 month. The applicant shall specify the quantity in accordance with business needs. A user may file applications for more than one withdrawal permit and have withdrawals divided among the permits.

(b) *Limitations on withdrawals.* A user holding a permit on Form 1450 (5150.13) may, during any month, withdraw not more than twice the number of proof gallons specified under paragraph (a) of this section, or 55 wine gallons (one drum), whichever is larger. The total quantity withdrawn annually may not exceed the number of proof gallons specified under paragraph (a) of this section for 1 month multiplied by 12 in a calendar year. Withdrawals are further subject to the following limitations:

(1) A user holding a withdrawal permit on Form 1450 (5150.13) authorizing withdrawals of not more than 240 proof gallons during a 12-month period, without bond, may not withdraw at one time a quantity which would result in there being more than 24 proof gallons on hand, in transit, and unaccounted for.

(2) A user (other than a State or political subdivision thereof, or the District of Columbia) holding a withdrawal permit on Form 4327 (5150.21) may not withdraw at one time a quantity which would result in there being more than 14 proof gallons on hand, in transit, and unaccounted for.

(3) A user who has filed bond, and a State, political subdivision thereof, or the District of Columbia, may not withdraw at one time a quantity which would result in there being on hand, in transit, and unaccounted for a quantity exceeding that stated in the application for permit under § 213.41 and § 213.41a, as applicable.

(c) *Exceptions to limitations.* (1) A user whose business is seasonal in nature, or who has other valid reasons, may request in the application for a withdrawal permit, a larger withdrawal during a specific calendar month or months; if so, the user's request shall be specific as to the amount desired.

(2) The user shall furnish sufficient information with the application to enable the regional regulatory administrator to evaluate the request for larger withdrawals.

(3) The limitations in paragraph (b) of this section on total withdrawals during the calendar year and on the quantity which may be on hand, in transit, and unaccounted for at any one time, apply to users granted larger withdrawals under this paragraph.

(Sec. 201, Pub. L. 85-859, 72 Stat. 1370, as amended (26 U.S.C. 5271))

**Par. 13.** Section 213.110 is revised to read as follows:

### § 213.110 Issuance and duration of withdrawal permits.

If the application submitted in accordance with § 213.109 is approved, the regional regulatory administrator shall issue the withdrawal permit on Form 1450 (5150.13) and forward the original to the permittee. If the application submitted in accordance with § 213.41a is approved, the regional regulatory administrator shall issue the limited withdrawal permit on Form 4327 (5150.21) and forward the original to the permittee. Withdrawal permits on Forms 1450 (5150.13) and 4327 (5150.21) shall have the same duration as industrial use permits in accordance with § 213.45.

### § 213.111 [Removed]

**Par. 14.** Section 213.111 is removed.

### § 213.114 [Amended]

**Par. 15.** Section 213.114 is amended by revising the last sentence to read as follows: "When space for making entries on withdrawal permit forms is no longer available, separate sheets, as needed, shall be attached to and made part of the form, and entries covering each shipment shall be made on them in the same manner as on the form."

### § 213.173 [Amended]

**Par. 15.** Section 213.173 is amended by deleting the words ", together with his renewal application, Form 1450, if any," from the last sentence.

Signed: May 5, 1982.

**W. T. Drake,**

*Acting Director.*

Approved: May 13, 1982.

**John M. Walker, Jr.,**

*Assistant Secretary (Enforcement and Operations).*

[FR Doc. 82-14210 Filed 5-21-82; 8:45 am]

BILLING CODE 4810-31-M

## DEPARTMENT OF THE INTERIOR

## Geological Survey

## 30 CFR Parts 211, 221, 231, 250, and 270

## Assessment of Late Payment or Underpayment Charges for Payments Received After Date Due or Underpaid on Federal Onshore, Offshore, and Indian Minerals Royalties

**AGENCY:** Minerals Management Service, Interior.

**ACTION:** Final rulemaking.

**SUMMARY:** These final rules amend the regulations regarding charges for late payments on Federal and Indian minerals royalties. These rules incorporate appropriate suggestions received as comments on the interim and proposed rules. The calculation method used in computing late payment charges has been clarified. The method will apply uniformly to all onshore and offshore Federal lands minerals leases and to Indian lands minerals leases (except Osage Indian Reservation) unless proscribed by other contractual or regulatory provisions. Late payment or underpayment charges will be assessed for the actual number of delinquent days, using the Treasury Department's "Current Value of Funds Rate" for the calculation of charges. The effect of this action is to establish late payment charges consistent with the Government's overall cash management policy.

**EFFECTIVE DATE:** June 1, 1982.

**FOR FURTHER INFORMATION CONTACT:** Raymond A. Hicks, Chief, Branch of Rules and Procedures for Royalty

Management, Minerals Management Service, 12203 Sunrise Valley Drive, Reston, VA 22091, (703) 860-7311, (FTS) 928-7311.

**SUPPLEMENTARY INFORMATION:**

## Background

Minerals Management Service (MMS), formerly the Conservation Division of the U.S. Geological Survey (USGS), is now publishing final rules. On December 23, 1980, the USGS had previously published interim late payment regulations applicable to the mineral resource payments from leases or contracts for Federal lands and Indian lands (45 FR 84762 et seq.). An identical rule was proposed for the Outer Continental Shelf (OCS) lands to make the rule for offshore operations consistent with the final rules for onshore operations (45 FR 84824).

Effective for onshore minerals in 1981, the current rules established late payment charges that are computed on the basis of the amount past due for each 30-day period or portion thereof that the payment was late. The phrase "or portion thereof" has resulted in many lessees/operators/payors interpreting the regulations to mean the actual number of days between the date due and the date that the payment was received at USGS. However, the USGS and MMS have interpreted the language "30-day period or portion thereof" to mean that the full charge will also be applicable to periods of less than 30 days.

The confusion that has resulted from contrary interpretations of the rule has resulted in an accumulation of numerous improperly computed late payment charges, and in protests of amounts billed. The resulting disorder places an undue burden on the payors and on MMS who are both concerned with accurate determination of charges due.

Numerous comments were received by USGS from lessees/operators/payors nationwide recommending that late payment charges be computed for the actual number of days that payments are delinquent. Additional commenters questioned exactly when payments must be received in order to avoid late payment charges. After reviewing those comments and other considerations, MMS has determined that a burden can be lifted from both MMS and payors by clarifying the regulations applicable to the assessment of late payment charges.

The final rules require that charges for late payments or underpayments be calculated from (but not including) the date due until and on the day on which the payment is received in the appropriate accounting office. Payments received after 4 p.m. local time will be acknowledged as received on the following workday. When the date due for payment occurs on a non-workday, the payment will be considered timely if it is appropriately received during business hours until 4 p.m. local time on the next workday after the date due.

It is the responsibility of each payor to submit all payments with sufficient lead time for it to arrive timely in the appropriate accounting office regardless of the method used to deliver the payment. Unusual circumstances may occasionally cause the delay of the arrival of a payment by the date due even though ample time has been allowed for normal delivery. In these cases, MMS will consider the waiver of the late payment charge after reviewing the evidence of intended delivery as presented by the payor.

The payor will be required to submit independent documentary evidence to MMS that shows the payment was sent sufficiently in advance of the date due to be delivered timely. These would include (1) The lead time allowed for delivery; (2) the mode of delivery used; and (3) all other pertinent factors. Examples of acceptable evidence that might satisfy these requirements are: a dated U.S. Postal Service receipt for Express Mail, Registered Mail, or Certified Mail; a dated receipt from a commercial delivery service; or a dated receipt from a financial institution for an electronic funds transfer (EFT).

MMS may waive a late payment charge if in its judgment the evidence submitted by the payor justifies a waiver. MMS does *not* examine and *will not* consider the "postmark" on any mail.

(Note.—Mail for the Accounting Center at Denver, Colorado, is picked up from the U.S. Post Office at 6:30 a.m. each workday for delivery to the Accounting Center. Mail received at the Post Office too late to be included in the 6:30 a.m. pickup will be received by MMS on the next workday.)

In accordance with the terms of leases, contracts, and/or regulations, the failure to pay minerals royalties timely constitutes a default that could subject such leases or contracts to cancellation. The late payment charge as established herein is a lesser remedy in lieu of cancellation. The action is also consistent with the Government's overall cash management policy and is based on the authority of the Secretary of the Interior to promulgate rules needed to administer and manage the minerals resources of Federal and Indian lands.

Late payment charges are calculated on the basis of a percentage assessment rate. In the absence of a specific lease or contract provision prescribing a different rate, that percentage assessment rate is calculated by the Department of the Treasury as an average of the "Current Value of Funds to Treasury." This quarterly rate is published prior to the first day of each calendar quarter for application to overdue payments or underpayments in the new calendar quarter. The rate is published in the Notices section of the **Federal Register** and indexed under "Fiscal Service/Notices/Funds Rate; Treasury Current Value." For example, the applicable rate of 14.39% for the first quarter of 1982 (January 1-March 31) was published as a Notice on December 16, 1981 (46 FR 61383).

Whenever any amounts are past due for periods of time that overlap calendar quarters, it is necessary to calculate the late payment charges by using the quarterly interest rates that existed during the several periods within the whole late period. For example, the rate was 18.35% for the calendar quarter ending December 31, 1981, and 14.39% for the calendar quarter ending March 31, 1982. Assuming a royalty payment due on November 30, 1981, and received by 4 p.m. local time on January 11, 1982, MMS would have recorded that overdue payment as received 42 days late. Thus, calculated by the procedure herein established, the delinquent payor would be assessed late payment charges for 31 days at the rate of 18.35% per annum, and for 11 days at the rate of 14.39% per annum.

From their effective date, these regulations apply to all late payments and to most underpayments, but exceptions to this policy may be granted to payors who have set up an advance payment plan with MMS under recently developed MMS procedures. However, if any late payment charge is not received by the date due, additional late payment charges will be assessed.

## Discussion of Comments

We received comments from 13 groups or individuals during the comment period for the interim, proposed rule. They included representatives of the Indian tribes, the oil and gas industry, the mining industry, and offices within the Department, as well as the public.

Several commenters suggested that adoption of a "grace period" during which late payment charges would not be assessed. These commenters felt that such a period was needed to allow for circumstances beyond the control of the payor. However, the language in the leases, contracts, and regulations is

specific on the date due. We do not agree that an automatic grace period is allowable. MMS may consider relief on a case-by-case basis because of unusual delays.

Several commenters suggested using the postmark as the date of receipt rather than the date on which payments are received by the appropriate accounting office. Some commenters stated that postmarked mail is accepted for dating the receipt of payments at other governmental agencies, such as the Internal Revenue Service. The establishment of dates due for other governmental agencies are administrative determinations by those agencies. Moreover, in keeping with the Government's overall cash management policy MMS must receive payments on or before the dates due. Therefore, MMS will not consider the postmark date as proof of timely payment.

Some commenters alleged that the current payment schedule does not allow sufficient time for gathering complex production and sales data needed to compute and remit royalty payments by the date due. They suggested that payments be scheduled to fall due at least 60 days after the end of the production month in order to avoid the assessment for unavoidable late payment charges. MMS has already addressed that issue and is considering development of a voluntary 2-month reporting and paying procedure, which is being separately proposed in a notice in the Federal Register.

Some commenters requested that the term "underpayment" be defined further and especially that the language in the preamble be clarified regarding "most underpayments" when referring to the assessment of late payment charges. An underpayment is any payment that is received when due but does not fully satisfy or cover the amount due. "Most underpayments" refers to those estimated payments on natural gas production that are made timely and in accordance with instructions provided by MMS to a payor but are not sufficient to cover the royalties actually due.

As was mentioned previously, many commenters recommended that the late payment charges be computed for the actual number of days that payments are delinquent. MMS is adopting that recommendation.

A few commenters suggested exempting from late payment charges those underpayments resulting from retroactive price changes by the Federal Energy Regulatory Commission or any other Federal agency. MMS agrees that a late payment charge should not be assessed retroactively. However, late payment charges will be assessed on underpayments due to retroactive price changes if adjusted payments are not received by the last day of the month after the month in which the price changes are made public and published.

A few commenters suggested extending the date due for initial payment of first production from 60 days as provided by NTL-1 and NTL-1A to 90 days. The commenters stated that although the Federal Government's share of production may be known, additional time is needed because other overriding royalties or other interests must frequently be accommodated. We do not agree that it is necessary to withhold the Federal Government's or Indians' share pending resolution of other royalty interests. We are not adopting this recommendation.

In the preamble to the interim rulemaking we stated that "* * * in the final rulemaking, consideration also will be given to revising the methodology required by 30 CFR 250.49 (rental and royalty payments, Outer Continental Shelf Lands) with respect to late payment charges so that such methodology will be consistent with that which is established with onshore minerals * * *" The current rulemaking does. It provides for the assessment of late payment charges in the same manner for both onshore and offshore operations.

Some commenters stated that interest ought to be paid by the Government to payors for overpayments at the same rate that interest is charged to delinquent payors by the Government. MMS does not agree. It is a general rule of law that in the absence of a contract or a statute to the contrary, interest cannot be paid on amounts owed by the Government.

There were numerous comments regarding various applications of late payment charges for late payments and underpayments of Indian minerals royalties. Many commenters stated that the rate established by interim regulation was too low and does not adequately reflect the current value of funds to the Indians. These commenters felt that Indian minerals owners are entitled to fair return on the use of their money and should receive at least the prime rate or the highest rate paid by most creditworthy corporate borrowers plus two points. Other commenters suggested that the "interest" to be charged for late payment of royalties for Indian minerals should be based either on the prime rate current at the time of the late payment or on the highest Certificate of Deposit rate current and being received by the Bureau of Indian Affairs for tribal investments. MMS is aware that the Department's trust responsibility to the Indians must assure that they receive a fair return on the sale of their minerals as well as a fair return on the use of their monies when payments are not made timely. MMS agrees that the Indians have a right to establish the rate to be used for assessing late payment charges on late payments or underpayments of their royalties. MMS has tentatively agreed to publish a rate separately established for the Indians in subsequent revisions to these regulations. However, until then MMS will continue to apply the rate prescribed in these regulations, except where other rates are specifically prescribed by lease or contract.

Several commenters requested that the regulatory language in 30 CFR Parts 211, 221, and 231 specify that late or underpayment charges collected by MMS be paid to the Indians. They requested that late payment charges assessed with respect to any Indian lease, permit, or contract shall be paid to the Indian or tribe to which the amount overdue is owed. We agree and have included such a provision in these rules.

Some commenters suggested that a penalty plus interest should be imposed for late payments and underpayments of Indian royalties. As we stated earlier, MMS plans to propose regulations that address such issues.

Some commenters opposed the suggestion that a future rulemaking be considered that would allow for recoupment of administrative costs incurred for securing compliance from delinquent payors. We assert however that the failure to report and pay timely, completely, and accurately results in considerable extra cost to the Government. Although we are not adopting such a recoupment rule at this time, we may in the future propose such a rule.

Some commenters suggested that the date due for annual minimum royalty payments needs to be defined. We agree and propose to develop separately a rule that will specify exactly when the minimum royalty must be paid after the expiration of the lease year.

Some commenters suggested that when a dispute arises between a payor and the Minerals Management Service regarding royalties, no late payment charge should be imposed until the dispute has been finally resolved. MMS does not agree because postponement of collection of a late payment charge would deprive the Government or Indians of the use of the monies due during the duration of the dispute. Moreover, such procedure would not be

in accordance with Federal cash management policy.

A few commenters suggested charging a fee equal to the original payment for all underpayments or late payments and/or cancellation for breach of contract if such violations continued. MMS does not agree. We believe that this regulation is an adequate deterrent and provides a lesser remedy than would cancellation.

Author: Raymond A. Hicks, Chief, Branch of Rules and Procedures for Royalty Management, Minerals Management Service, 12203 Sunrise Valley Drive, Reston, VA 22091 (703) 860-7311.

The Department of the Interior has determined that this document is not a major rule under Executive Order 12291 and certifies that this document will not have a significant economic effect on a substantial number of small entities under the Regulatory Flexibility Act (5 U.S.C. 601 et seq.) because during 1981 the Department collected less than $1 million in late or underpayment charges. This rule does not contain information collection requirements that require approval by the Office of Management and Budget under 44 U.S.C. 3507.

**List of Subjects in 30 CFR Parts 211, 221, 231, 250, 270**

Mineral royalties, Reporting requirements.

Under the authority of The Mineral Leasing Act, the Act of February 25, 1920, (30 U.S.C. 181 et seq.); the Acquired Lands Leasing Act of August 7, 1947, (30 U.S.C. 351 et seq.); the Geothermal Steam Act of 1970 (30 U.S.C. 1001 et seq.); the Outer Continental Shelf Lands Act, (43 U.S.C. 1801 et seq.); the Allotted Lands Leasing Act of 1909, (25 U.S.C. 396); and the Tribal Lands Act of 1938, (25 U.S.C. 396a); and (25 U.S.C. 396a); and E.O. 12291 (46 FR 13193) Title 30 CFR Chapter II is amended as set forth below:

Dated: May 4, 1982.

**Daniel N. Miller, Jr.,**

*Assistant Secretary of the Interior.*

## PART 211—COAL MINING OPERATING REGULATIONS

Section 211.67 of Title 30 of the Code of Federal Regulations is revised to read as follows:

**§ 211.67 Late payment or underpayment charges.**

(a) The failure to make timely or proper payment of any monies due pursuant to leases and contracts subject to these regulations will result in the collection by the Minerals Management Service (MMS) of the full amount past due plus a late payment charge. Exceptions to this late payment charge may be granted when estimated payments on minerals production have already been made timely and otherwise in accordance with instructions provided by MMS to the payor. However, late payment charges assessed with respect to any Indian lease, permit, or contract shall be collected and paid to the Indian or tribe to which the amount overdue is owed.

(b) Late payment charges are assessed on any late payment or underpayment from the date that the payment was due until the date on which the payment is received in the appropriate MMS accounting office. Payments received after 4 p.m. local time on the date due will be acknowledged as received on the following workday.

(c) Late payment charges are calculated on the basis of a percentage assessment rate. In the absence of a specific lease, permit, license, or contract provision prescribing a different rate, this percentage assessment rate is prescribed by the Department of the Treasury as the "Treasury Current Value of Funds Rate."

(d) This rate is available in the Treasury Fiscal Requirements Manual Bulletins that are published prior to the first day of each calendar quarter for application to overdue payments or underpayments in the new calendar quarter. The rate is also published in the Notices section of the **Federal Register** and indexed under "Fiscal Service/Notices/Funds Rate; Treasury Current Value."

(e) Late payment charges apply to all underpayments and payments received after the date due. These charges include production, minimum, or advance royalties; assessments for liquidated damages; or any other payments, fees, or assessments that a lessee/operator/payor is required to pay by a specified date. The failure to pay past due payments, including late payment charges, will result in the initiation of other enforcement proceedings.

## PART 221—OIL AND GAS OPERATING REGULATIONS

Section 221.80 of Title 30 of the Code of Federal Regulations is revised to read as follows:

**§ 221.80 Late or underpayment charges.**

(a) The failure to make timely or proper payments of any monies due pursuant to leases, permits, and contracts subject to these regulations will result in the collection by the Minerals Management Service (MMS) of the full amount past due plus a late payment charge. Exceptions to this late payment charge may be granted when estimated payments on minerals production have already been made timely and otherwise in accordance with instructions provided by MMS to the payor. However, late payment charges assessed with respect to any Indian lease, permit, or contract shall be collected and paid to the Indian or tribe to which the amount overdue is owed.

(b) Late payment charges are assessed on any late payment or underpayment from the date that the payment was due until the date on which the payment is received in the appropriate MMS accounting office. Payments received after 4 p.m. local time on the date due will be acknowledged as received the following workday.

(c) Late payment charges are calculated on the basis of a percentage assessment rate. In the absence of a specific lease, permit, license, or contract provision prescribing a different rate, this percentage assessment rate is prescribed by the Department of the Treasury as the "Treasury Current Value of Funds Rate."

(d) This rate is available in Treasury Fiscal Requirements Manual Bulletins that are published prior to the first day of each calendar quarter for application to overdue payments or underpayments in that new calendar quarter. The rate is also published in the Notices section of the **Federal Register** and indexed under "Fiscal Service/Notices/Funds Rate; Treasury Current Value."

(e) Late payment charges apply to all underpayments and payments received after the date due. These charges include production and minimum royalties; assessments for liquidated damages; administrative fees and payments by purchasers of royalty taken-in-kind; or any other payments, fees, or assessments that a lessee/operator/permittee/payor/royalty taken-in-kind purchaser is required to pay by a specified date. The failure to pay past due amounts, including late payment charges, will result in the initiation of other enforcement proceedings.

## PART 231—OPERATING REGULATIONS FOR EXPLORATION, DEVELOPMENT, AND PRODUCTION

Section 231.80 of Title 30 of the Code of Federal Regulations is revised to read as follows:

**§ 231.80 Late payment or underpayment charges.**

(a) The failure to make timely or proper payments of any monies due pursuant to leases, permits, and contracts subject to these regulations will result in the collection by the Minerals Management Service (MMS) of the amount past due plus a late payment charge. Exceptions to this late payment charge may be granted when estimated payments have already been made timely and otherwise in accordance with instructions provided by MMS to the payor. However, late payment charges assessed with respect to any Indian lease, permit, or contract shall be collected and paid to the Indian or tribe to which the overdue amount is owed.

(b) Late payment charges are assessed on any late payment or underpayment from the date that the payment was due until the date on which the payment is received in the appropriate MMS accounting office. Payments received after 4 p.m. local time on the date due will be acknowledged as received on the following workday.

(c) Late payment charges are calculated on the basis of a percentage assessment rate. In the absence of a specific lease, permit, license, or contract provision prescribing a different rate, this percentage assessment rate is prescribed by the Department of the Treasury as the "Treasury Current Value of Funds Rate."

(d) This rate is available in the Treasury Fiscal Requirements Manual Bulletins that are published prior to the first day of each calendar quarter for application to overdue payments or underpayments in that new calendar quarter. The rate is also published in the Notices section of the **Federal Register** and indexed under "Fiscal Service/Notices/Funds Rate; Treasury Current Value."

(e) Late payment charges apply to all underpayments and payments received after the date due. These charges include rentals; production, minimum, or advance royalties; assessments for liquidated damages; administrative fees and payments by purchaser of royalty taken-in-kind or any other payments, fees, or assessments that a lessee/operator/permittee/payor/or purchaser of royalty taken-in-kind is required to pay by a specified date. The failure to pay past due amounts, including late payment charges, will result in the initiation of other enforcement proceedings.

## PART 250—OIL AND GAS AND SULPHUR OPERATIONS IN THE OUTER CONTINENTAL SHELF

Section 250.49 of Title 30 of the Code of Federal Regulations is revised to read as follows:

**§ 250.49 Royalties, net profit shares, and rental payments.**

(a) As specified under the provisions of the lease, the lessee shall pay all rental when due, and shall pay in value or deliver in production all royalties and net profit shares in the amounts of value or production determined by the Director to be due. Payments of rental, royalties, and net profit shares in value shall be by electronic transfer of funds or by check or draft on a solvent bank or by money order drawn to the order of the Minerals Management Service (MMS).

(b) The failure to make timely or proper payments of any monies due pursuant to leases, permits, and contracts subject to these regulations will result in the collection of the amount past due plus a late payment charge. Exceptions to this late payment charge may be granted when estimated payments on minerals production have already been made timely and otherwise in accordance with instructions provided by MMS to the payor.

(c) Late payment charges are assessed on any late payment or underpayment from the date that the payment was due until the date on which the payment is received in the appropriate MMS accounting office. Payments received after 4 p.m. local time on the date due will be acknowledged as received on the following workday.

(d) Late payment charges are calculated on the basis of a percentage assessment rate. In the absence of a specific lease, permit, license, or contract provision prescribing a different rate, this percentage assessment rate is prescribed by the Department of the Treasury as the "Treasury Current Value of Funds Rate."

(e) This rate is available in Treasury Fiscal Requirements Manual Bulletins that are published prior to the first day of each calendar quarter for application to overdue payments or underpayments in the new calendar quarter. The rate is also published in the Notices section of the **Federal Register** and indexed under "Fiscal Service/Notices/Funds Rate; Treasury Current Value."

(f) Late payment charges apply to all underpayments and payments received after the date due. These charges include production and minimum royalties; assessments for liquidated damages; administrative fees and payments by purchasers of royalty taken-in-kind; or any other payments, fees, or assessments that a lessee/operator/payor/permittee/royalty taken-in-kind purchaser is required to pay by a specified date. The failure to pay past due amounts, including late payment charges, will result in the initiation of other enforcement proceedings.

## PART 270—GEOTHERMAL RESOURCES OPERATIONS ON PUBLIC, ACQUIRED, AND WITHDRAWN LANDS

Section 270.81 of Title 30 of the Code of Federal Regulations is revised to read as follows:

**§ 270.81 Late payment or underpayment charges.**

(a) The failure to make timely or proper payment of any monies due pursuant to leases and contracts subject to these regulations will result in the collection by the Minerals Management Service (MMS) of the full amount past due plus a late payment charge. Exceptions to this late payment charge may be granted when estimated payments on minerals production have already been made timely and otherwise in accordance with the instructions provided by the MMS to the payor.

(b) Late payment charges are assessed on any late payment or underpayment from the date that the payment was due until the date on which the payment is received in the appropriate MMS accounting office. Payments received after 4 p.m. local time on the date due will be acknowledged as received on the following workday.

(c) Late payment charges are calculated on the basis of a percentage assessment rate. In the absense of a specific lease, permit, license, or contract provision prescribing a different rate, this percentage assessment rate is prescribed by the Department of the Treasury as the "Treasury Current Value of Funds Rate."

(d) This rate is available in the Treasury Fiscal Requirements Manual Bulletins that are published prior to the first day of each calendar quarter for application to overdue payments or underpayments in that new calendar quarter. The rate is also published in the Notices section of the **Federal Register** and indexed under "Fiscal Service/Notices/Funds Rate; Treasury Current Value."

(e) Late payment charges apply to all underpayments and payments received after the date due. These charges

include production, minimum, and compensatory royalties; assessments for liquidated damages; administrative fees and payments by purchasers of royalty taken-in-kind; or any other payments, fees, or assessments that a lessee/operator/payor/royalty taken-in-kind purchaser is required to pay by a specified date. The failure to pay past due payments, including late payment charges, will result in the initiation of other enforcement proceedings.

[FR Doc 82-14227 Filed 5-24-82; 8:45 am]
BILLING CODE 4310-MR-M

## DEPARTMENT OF DEFENSE

## Office of the Secretary

## 32 CFR Part 373

**[DoD Directive 5148.10][1]**

## Assistant to the Secretary of Defense (Review and Oversight)

**AGENCY:** Office of the Secretary of Defense, DoD.

**ACTION:** Final rule.

**SUMMARY:** The Secretary of Defense has assigned responsibilities and functions to the Assistant to the Secretary of Defense (Review and Oversight) (ATSD (R&O)), and has delegated specific authorities. This rule (DoD Directive 5148.10) serves as the instrument that authorizes the ATSD(R&O), to carry out his charter.

**EFFECTIVE DATE:** This rule was approved and signed by the Deputy Secretary of Defense on April 20, 1981, and is effective as of that date.

**FOR FURTHER INFORMATION CONTACT:** Mr. Arthur H. Ehlers, Director for Organizational and Management Planning, Office of the Deputy Secretary of Defense (Administration), The Pentagon, Washington, D.C. 20301, Telephone 202-695-4278.

**SUPPLEMENTARY INFORMATION:** This information is submitted in compliance with the requirements of section 552(a)(1) of Title 5, United States Code, and 1 CFR 305.76.

### List of Subjects in 32 CFR Part 373

Organization and functions (government agencies), Investigations.

Accordingly, 32 CFR, Chapter 1, is amended by adding a new Part 373, reading as follows:

[1] Copies may be obtained, if needed, from the U.S. Naval Publications and Forms Center, 5801 Tabor Avenue, Philadelphia, PA 19120 Attention: Code 301.

## PART 373—ASSISTANT TO THE SECRETARY OF DEFENSE (REVIEW AND OVERSIGHT)

Sec.
373.1 Purpose.
373.2 Definitions.
373.3 Responsibilities.
373.4 Relationships.
373.5 Authorities.

Authority: 10 U.S.C., Chapter 4.

### § 373.1 Purpose.

Pursuant to the authority vested in the Secretary of Defense under the provisions of title 10, United States Code, the position of Assistant to the Secretary of Defense (Review and Oversight) (ATSD(R&O)), is hereby established with the responsibilities, functions, and authorities prescribed herein.

### § 373.2 Definitions.

The term "DoD Components" refers to the Office of the Secretary of Defense and its field activities, the Military Departments, the Organization of the Joint Chiefs of Staff, the Unified and Specified Commands, and the Defense Agencies.

### § 373.3 Responsibilities.

The ATSD(R&O) shall serve as the principal advisor and assistant to the Secretary of Defense for matters related to the combatting of fraud, waste, and abuse in DoD programs and operations. In carrying out these responsibilities, the ATSD(R&O) shall:

(a) Develop policy, monitor and evaluate program performance, and provide guidance to DoD Components on matters regarding criminal investigation programs.

(b) Monitor and evaluate the adherence of DoD Components to internal audit, contract audit, and internal review principles, policies, and procedures. Identify instances of non-compliance and recommend appropriate corrective actions to the Secretary of Defense or the responsible DoD Component Head.

(c) Develop policy, evaluate program performance, and monitor follow-up actions taken by DoD Components in response to GAO audit, internal audit, contract audit, and internal review reports. Identify those cases in which audit recommendations capable of significantly improving the economy, efficiency, and effectiveness of DoD programs and operations have been ignored or circumvented. Recommend corrective action to the Secretary of Defense or the responsible DoD Component Head.

(d) Advise the Secretary of Defense of any incidents of fraud, waste, or abuse in DoD programs and operations which require the Secretary's personal attention.

(e) Exercise direction, authority and control over the Defense Audit Service (DoD Directive 5105.48).[1]

(f) Perform such other duties as the Secretary of Defense may prescribe.

### § 373.4 Relationships.

(a) In the performance of assigned duties, the ATSD(R&O) shall:

(1) Coordinate actions with the ASD (Comptroller), DoD General Counsel, and other DoD organizations having collateral or related functions.

(2) Maintain liaison with DoD Components and other governmental and nongovernmental agencies for the exchange of information and advice on programs in the field of assigned responsibilities and functions.

(3) Make use of established facilities and services in the Department of Defense or other governmental agencies to avoid duplication and achieve maximum efficiency and economy.

(b) Heads of DoD Components shall coordinate with the ATSD(R&O) on all matters relating to the functions and responsibilities cited in § 373.3.

### § 373.5 Authorities.

The ATSD(R&O) is hereby delegated authority to:

(a) Issue instructions and one-time, directive-type memoranda which carry out policies approved by the Secretary of Defense in the field of assigned responsibilities and functions. Instructions to the Military Departments will be issued through the Secretaries of those Departments or their designees. Instructions to Unified and Specified Commands will be issued through the Joint Chiefs of Staff.

(b) Obtain such reports, information, advice, and assistance consistent with the policies and criteria of DoD Directive 5000.19,[1] "Policies for the Management and Control of Information Requirements," March 12, 1976, as deemed necessary.

(c) Communicate directly with heads of DoD organizations, including the Secretaries of the Military Departments, the Joint Chiefs of Staff, the Commanders of the Unified and Specified Commands, and the Directors of Defense Agencies. Communications with the Commanders of the Unified and Specified Commands shall be

coordinated with the Joint Chiefs of Staff.

M. S. Healy,

*OSD Federal Register Liaison Officer, Department of Defense.*

May 20, 1982.

[FR Doc. 82-14216 Filed 5-24-82; 8:45 am]

BILLING CODE 3810-01-M

## 32 CFR Part 374

**[DoD Directive 5105.50] [1]**

## Defense Criminal Investigative Service

**AGENCY:** Office of the Secretary of Defense, DoD.

**ACTION:** Final rule.

**SUMMARY:** Under the authority of Part 373 of this title, the Defense Criminal Investigative Service (DCIS) is established to investigate criminal or fraudulent activities involving DoD Components or DoD contractors. This rule (DoD Directive 5105.50) serves as the instrument that authorizes the Director, DCIS, to carry out his charter.

**EFFECTIVE DATE:** This rule was approved and signed by the Deputy Secretary of Defense on April 28, 1982, and is effective as of that date.

**FOR FURTHER INFORMATION CONTACT:** Mr. William G. Dupree, Deputy Director, DCIS, Cameron Station, Alexandria, Virginia, 22314, Telephone 202-274-5360.

**SUPPLEMENTARY INFORMATION:** This information is submitted in compliance with the requirements of section 552(a)(1) of Title 5, United States Code, and 1 CFR 305.76.

### List of Subjects in 32 CFR Part 374

Organization and functions (government agencies), Investigations

Accordingly, 32 CFR, Chapter 1, is amended by adding a new Part 374, reading as follows:

## PART 374—DEFENSE CRIMINAL INVESTIGATIVE SERVICE

Sec.



**Authority:** 10 U.S.C., Chapter 4.

[1] Copies may be obtained, if needed, from the U.S. Naval Publications and Forms Center, 5801 Tabor Avenue, Philadelphia, PA 19120. Attention: Code 301.

### § 374.1 Purpose.

Under the authority of Part 373 of this title, this part establishes the Defense Criminal Investigative Service (DCIS), assigns responsibilities, and defines functions and organization of the DCIS.

### § 374.2 Applicability.

The provisions of the part apply to the Office of the Secretary of Defense (OSD), the Military Departments, the Organization of the Joint Chiefs of Staff, the Unified and Specified Commands, and the Defense Agencies (hereafter referred to as "DoD Components").

### § 374.3 Definitions.

(a) *DoD Contractor.* An individual, corporation, or other commercial or nonprofit entity, their employees or agents, who contract or negotiate with a DoD Component to supply goods or services.

(b) *Investigations.* Investigations of suspected criminal activities and other actions intended to detect violations of major federal criminal statutes including felonies punishable under the UCMJ, U.S.C. 10, Chapter 47; and violations of DoD Directives System issuances (DoD directives, instructions, regulations, and other policy and regulatory issuances) by civilian or military personnel assigned to the Office of the Secretary of Defense, Unified and Specified Commands, the Organization of the Joint Chiefs of Staff, and the Defense Agencies; and those individuals or contractors who are suspected of committing criminal violations against DoD personnel or property.

### § 374.4 Policy.

(a) The DCIS is established as a worldwide civilian federal law enforcement activity to investigate criminal fraudulent activities involving DoD Components or DoD contractors within the 50 states, the District of Columbia, the Commonwealth of Puerto Rico, and in other nations.

(b) To avoid duplication of efforts, DCIS will refer to the respective Military Departments' investigative jurisdiction matters involving the personnel, property, facilities, or contracts both awarded and administered by a single Military Department, unless otherwise directed by the Secretary of Defense or the Assistant to the Secretary of Defense (Review and Oversight).

### § 374.5 Responsibilities.

(a) The Assistant to the Secretary of Defense (Review and Oversight) (ATSD(R&O)) shall:

(1) Authorize the Director, DCIS, to investigate allegations of criminal activities and other suspected violations by civilian or military personnel assigned to DoD Components and conduct other investigations into suspected criminal violations against DoD personnel or property.

(2) Conduct timely investigations pertaining to matters of interest to the Secretary of Defense.

(b) The Director, Defense Criminal Investigative Service, shall:

(1) Conduct criminal investigations involving criminal activity or violations of major federal criminal offenses or major violations of the UCMJ, U.S.C. 10, Chapter 47 within the Office of the Secretary of Defense, the Organization of Joint Chiefs of Staff, the Unified and Specified Commands, and the Defense Agencies.

(2) Conduct criminal investigations of those individuals or contractors suspected of committing criminal violations against DoD personnel or property.

(3) Conduct criminal investigations involving the personnel, property, or facilities of a Military Department involving multiservice awarded or administered contracts.

(4) Conduct joint investigations of criminal matters with other military or civilian investigative agencies.

(5) Refer any criminal matter principally involving a single Military Department to its investigative organization unless otherwise directed by the Secretary of Defense or the ATSD(R&O).

(6) Refer to the appropriate civilian and military investigative or intelligence agency information pertaining to intelligence or counterintelligence matters.

(7) Organize, direct, and manage the DCIS to include the selection of all personnel for appointment to DCIS.

(8) Conduct fraud and crime prevention surveys within his areas of responsibility, and as directed, for the purpose of detecting criminal activity, identifying, minimizing, or eliminating systemic weaknesses conducive to criminal activity.

(9) Provide, as necessary, programing and workload projections to the Military Departments.

(10) Perform other duties and conduct other investigations, operations, protective services, or projects as directed by the Secretary of Defense, the ATSD(R&O), or their designees.

(c) The Secretaries of the Military Departments, of designees, shall ensure that their military investigative organizations will be responsive to DCIS lead requests in geographic areas where DCIS lacks resources.

(d) Heads of DoD Components shall provide to the Director, DCIS, access to information the DCIS requires to carry out its responsibilities, and shall provide the DCIS final disposition or actions taken based upon DCIS investigations.

**§ 374.6 Organization and Management.**

(a) The DCIS is a separately organized activity of the Department of Defense under the direction, authority, and control of the ATSD(R&O).

(b) The DCIS is assigned to the Defense Audit Service for administrative purposes; but the Director, DCIS, shall report directly to the ATSD(R&O).

(c) The DCIS shall be headed by a civilian director, who shall also hold the position of Deputy Assistant to the Secretary of Defense (Criminal Investigations), and who shall be selected by the ATSD(R&O).

(d) The DCIS shall be authorized such personnel, facilities, funds, and other resources as determined by the Secretary of Defense and the ATSD(R&O).

(e) The Director, DCIS, shall establish, within assigned resources, subordinate organizational elements within the 50 states, the District of Columbia, the Commonwealth of Puerto Rico, and other nations.

(f) The Director, DCIS, has authority to enter into Memoranda of Understanding with appropriate DoD Components arranging investigative support in those geographical or functional areas where DCIS does not have resources available.

(g) Administrative support for the DCIS will be provided by other DoD Components in accordance with DoD interservice support agreements.

**§ 374.7 Relationships.**

(a) In the performance of assigned responsibilities, the Director, DCIS, shall:

(1) Maintain liaison and coordinate with DoD Components and other federal, state, and local agencies.

(b) Heads of DoD Components, except Military Departments, shall refer immediately to the DCIS all incidents of actual, suspected, or alleged criminal offenses for investigative action or for referral to the Military Department concerned, civilian investigative agency, or the Federal Bureau of Investigation (FBI).

**§ 374.8 Procedures.**

(a) DCIS criminal investigators, in carrying out investigations and related activities, shall be issued standardized credentials and badges designating them as "special agents." Personnel who are issued DCIS special agent credentials are cleared for access up to and including top secret and are presumed to have a need to know with regard to access to information, material, or spaces relevant to the performance of their official duties.

(b) Access to special intelligence and compartmented or similarly controlled materials, spaces, or information shall be subject to clearance by the controlling authority before the special agent pursues a matter of official concern.

(c) DCIS special agent credentials are to be given full recognition when presented upon entering or leaving DoD installations.

(d) DCIS personnel and vehicles used by them in the course of official business, and all occupants therein shall be exempt from routine search.

**§ 374.9 Authority.**

(a) The Director, DCIS, shall have authority for selection of personnel for appointment to the DCIS.

(b) The Director, DCIS, is specially delegated authority to:

(1) Obtain reports, information, advice, and assistance, consistent with the policies and criteria of DoD Directives 5000.19,[1] "Policies for the Managment and Control of Information Requirements," March 12, 1976 and DoD Directive 5000.11, "Data Elements and Data Codes Standardization Program," December 7, 1964, that may be necessary for the performance of assigned mission, functions, and responsibilities.

(2) Communicate directly with appropirate personnel of other DoD Components and other government agencies on matters related to the mission and programs of the DCIS.

(3) Exercise the administrative authorities set forth in § 374.10.

**§ 374.10 Delegations of authority.**

Pursuant to the authority vested in the Secretary of Defense, and subject to his direction, authority, and control, and in accordance with DOD policies, directives, and instructions, the Director, DCIS, or his designee, is hereby delegated authority, as required in the administration and operation of DCIS, to:

(a) In accordance with the provisions of 5 U.S.C. Section 7532; E.O. 10450, and 32 CFR 156.

(1) Designate Positions as "sensitive;"

(2) Authorize, in case of an emergency, the appointment to a sensitive position, for a limited period of time, of a person for whom a full field investigation or other appropriate investigation, including the National Agency Check, has not been completed; and

(3) Authorize the suspension, but not terminate the service, of an employee in the interest of national security.

(b) Authorize and approve overtime work for civilian officers and employees in accordance with the provisions of 5 U.S.C. Subchapter V, Chapter 55 and applicable regulations.

(c) Authorize and approve travel for DCIS personnel in accordance with Joint Travel Regulations, Volume 2. Authorize and approve temporary duty travel only for military personnel assigned or detailed to DCIS in accordance with Joint Travel Regulations, Volume 1.

(d) Develop, establish, and maintain an active and continuing records management program, consistent with DOD Directive 5015.21, "Records Management Program," September 17, 1980.

(e) Authorize the publication of advertisements, notices, or proposals in newspapers, magazines, or other public periodicals, consistent with 44 U.S.C. 3702.

(f) Establish and maintain, for the functions assigned, an appropriate publications system for the issuance of regulations, instructions reference documents, and changes thereto, consistent with the policies and procedures prescribed in DOD Directive 5025.11, "Department of Defense Directives System," October 16, 1980, and DOD 5025.1-M, "DOD Directives System Procedures," April 1981.

(g) Authorize DCIS personnel to carry firearms in accordance with DOD Directive 5210.66,[1] "Carrying of Firearms by Department of Defense Personnel," May 31, 1979.

May 20, 1982.

**M. S. Healy,**

*OSD Federal Register Liaison Office, Department of Defense.*

[FR Doc. 82-14215 Filed 5-24-82; 8:45 am]

BILLING CODE 3810-01-M

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 52

**[A-7-FRL 2121-4]**

### Approval and Promulgation of Implementation Plans; Iowa

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Final Rulemaking (FRM).

[1] See footnote on page 1.

**SUMMARY:** Today EPA approves revised State air pollution control regulations as official parts of the Iowa State Implementation Plan. Approval means that the regulations will be enforceable against individual sources of air pollution by the federal government as well as by the state government.

The revisions include new continuous monitoring requirements for certain sources, more restrictive particulate emission limits for certain sources, and revised limits for metal finishing operations.

**DATES:** Effective date: July 26, 1982. This action will be effective 60 days from today unless notice is received within 30 days that someone wishes to submit adverse or critical comments.

**ADDRESSES:** Comments should be sent to Daniel J. Wheeler, Environmental Protection Agency, 324 East 11th Street, Kansas City, Missouri 64106. The state submission is available at the above address and at the Iowa Department of Environmental Quality, Henry A. Wallace Building, 900 East Grand, Des Moines, Iowa 50319; the Environmental Protection Agency, Public Information Reference Unit, Room 2922, 401 M Street SW., Washington, D.C. 20460; and the Office of the Federal Register, 1100 L Street, N.W., Room 8401, Washington, D.C. 20408.

**FOR FURTHER INFORMATION CONTACT:** Daniel J. Wheeler, 816 374-3791.

**SUPPLEMENTARY INFORMATION:** On June 20, 1977, the Iowa Department of Environmental Quality (DEQ) submitted proposed revisions to the Iowa SIP. These revisions were not acted on at the time because of their minor nature and the press of higher priority work. They are approved today as part of the agency effort to reduce the backlog of pending actions. The specific changes submitted by the state are described below.

In State Rule 400—4.3(2)b, "Combustion for Indirect Heating," paragraph (3) is revised to provide an emission limit of .2 pounds of particulate matter-per-million-British Thermal Units ($10^6$ BTU) of heat input for new sources of 150 to 250 $\times$ $10_6$ BTU per-hour-heat input. New sources of less than 150 $\times$ $10^6$ BTUs per hour remain limited to .6 lb. per $10^6$ BTU. These limits are based on Iowa's compliance testing method which catches approximately twice as much particulate as the standard EPA test method. Therefore, Iowa particulate limits are approximately equivalent to limits allowing emissions of only half as much. The Iowa definition of "new" refers to any equipment not under construction or for which components had not been purchased on or before September 23, 1970.

A new Rule 400—4.4(6), "Sand Handling and Surface Finishing Operations in Metal Processing" has been adopted. It places a limit of .05 grains of particulate matter-per-standard-cubic foot of exhaust gas on new equipment designed for sand shakeout, milling, molding, cleaning, preparation, reclamation, rejuvenation, abrasive cleaning, shot blasting, grinding, cutting, sawing, or buffing. It applies to new foundry and metal processing operations. For purposes of this rule only, "new" refers to equipment bought and installed after August 1, 1977.

Subrule 4.4(12), "Incinerators," is revised by deleting the reference to objectionable odors.

Chapter 7, "Measurement of Emissions," is completely revised. The State now requires the continuous monitoring of opacity from coal-fired steam generators and of sulfur dioxide from sulfuric acid plants. These are among the requirements of 40 CFR 51.19 as promulgated October 6, 1975 (40 FR 46247). The state has certified that there are no existing sources in Iowa in the other categories which are required to monitor by 40 CFR 51.19.

Chapter 7 also requires record keeping and reporting of continuous monitoring results. It specifies acceptable test procedures as those in the State's "Compliance Sampling Manual." Exemptions are provided for sources whose 1974 capacity factor was less than 30 percent, sources to be retired within 5 years and sources subject to New Source Performance Standards (NSPS). The last, of course, are subject to the monitoring requirements of the NSPS.

Sources which already have continuous monitors, but which do not meet the performance specifications for such monitors, have a 5-year exemption from installing equipment meeting specifications. The Executive Director of the DEQ may provide temporary exemptions for monitoring system breakdowns

The State has also revised Rule 3.1 "Permits," to require permits for anaerobic lagoons and added new Rule 4.5, "Odorous Substances," and subrule 14.3(3), "Odor Complaints and Violations." Rule 1.2, "Definitions," is amended by adding definitions of anaerobic lagoon, odor, odorous substance, and odorous substance source. The definition of objectionable odor is deleted and the subrules renumbered so that the definitions appear in alphabetical order. These revisions deal with the control of odor for which EPA has not adopted standards and does not require control. These revisions are unavoidably included with the SIP revisions but are not submitted by the state as part of the State plan and EPA does not take any action on them.

With the exception of the odor rules, the above rule changes constitute revisions to the Iowa SIP. The decision to approve these revisions was based on the determination that they meet the requirements of Section 110(a)(A) through (H) of the Clean Air Act and 40 CFR Part 51, "Requirements for Preparation, Adoption and Submittal of State Implementation Plans."

EPA is approving this change without prior notice and public comment because it is only approving provisions which are noncontroversial. The public is advised that this action will be effective 60 days from the date of the **Federal Register** notice. However, if notice is received within 30 days that someone wishes to submit adverse or critical comments, this action will be withdrawn and two subsequent notices will be published before the effective date. One notice will withdraw the final action and another will begin a new rulemaking by announcing a proposal of the action and establishing a comment period.

Under 5 U.S.C. Section 605(b), the Administrator has certified that SIP approvals do not have a significant economic impact on a substantial number of small entities. (See 46 FR 8709.)

The Office of Management and Budget has exempted this rule from the requirement of Section 3 of Executive Order 12291.

Under Section 307(b)(1) of the Clean Air Act, as amended, judicial review of this action is available only by the filing of a petition for review in the United States Court of Appeals for the appropriate circuit within 60 days of today. Under Section 307(b)(2), the requirements which are the subject of today's notice may not be challenged later in civil or criminal proceedings brought by the EPA to enforce these requirements.

List of Subjects in 40 CFR Part 52; Air pollution control, Ozone, Sulfur oxides, Nitrogen dioxide, Lead, Particulate matter, Carbon monoxide, Hydrocarbons.

This notice of final rulemaking is issued under the authority of Sections 110, and 301 of the Clean Air Act as amended (42 U.S.C. 7410 and 7601).

Dated: May 19, 1982.

Anne M. Gorsuch,

*Administrator.*

Note.—Incorporation by Reference of the State Implementation Plan for the State of Iowa was approved by the Director of the *Federal Register* on July 1, 1981.

## PART 52—APPROVAL AND PROMULGATION OF IMPLEMENTATION PLANS

Part 52 of Chapter I, Title 40 of the Code of Federal Regulations is amended as follows:

### Subpart Q—Iowa

1. Section 52.820 is amended by adding a new paragraph (c)(26a) following paragraph (c)(26) as follows:

**§ 52.820 Identification of Plan.**

* * * * *

(c) * * *

(26a) Revisions of Rules 1.2, 4.3(2)b, 4.4(6), 4.4(12) and of Chapter 7 of the Iowa Administrative Code relating to Air Pollution Control were submitted June 20, 1977, by the Department of Environmental Quality.

* * * * *

[FR Doc. 82-14169 Filed 5-24-82; 8:45 am]

BILLING CODE 6560-50-M

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Office of Community Services

### 45 CFR Parts 1050, 1067, and 1068

### Close Out of Grants Funded by the Community Services Administration

**AGENCY:** Office of Community Services, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Office of Community Services (OCS) is amending the regulations applicable to grants funded by the Community Services Administration (CSA). Congress abolished CSA effective October 1, 1981, and OCS is responsible for closing out the programmatic activities of CSA. To facilitate the orderly close-out and final audit of CSA grants which do not contain specific termination dates, the rule provides that these grants will expire at the close of each grantee's planned minimum funding period, and that expenses may not be incurred under a CSA grant subsequent to that date. OCS is also amending the regulation to require grantees to submit all audit reports within 60 days following the funding period, thereby expediting the conclusion of the close-out process.

**EFFECTIVE DATE:** June 24, 1982.

**FOR FURTHER INFORMATION CONTACT:** Mr. John C. Meyer, Office of Community Services, Department of Health and Human Services, 1200 19th Street NW., Washington, D.C. 20506; telephone 202-653-9233.

**SUPPLEMENTARY INFORMATION:**

### Legislative Background

Until October 1, 1981, CSA administered community services grant programs authorized under the Economic Opportunity Act of 1964 ("EOA"). The Omnibus Budget Reconciliation Act of 1981 (Pub. L. 97-35) ("OBRA") repealed most provisions of the EOA, abolished CSA, and created several block grant programs including the new Community Services Block Grant program to be administered by the Secretary of HHS through an Office of Community Services (OCS). Regulations implementing these block grants, which transfer substantial grant-making authority from the Federal Government to the States, were published in the **Federal Register** on October 1, 1981 (46 FR 48587).

In addition to administering the Community Services Block Grant program and certain discretionary community services grants, OCS is responsible for continuing the administration of the otherwise repealed community services programs during the Fiscal Year 1982 transition period in those states which have requested that direct federal funding of such programs be continued. Through a delegation of authority from the Director of the Office of Management and Budget, OCS must also terminate the affairs of CSA, including transferring or otherwise disposing of CSA grants and grant funds as necessary to effectuate the purposes of the block grant program. Pending audits of completed CSA grants must therefore be concluded, and grants with funding periods extending beyond September 30, 1981 must be closed out and audited. In Pub. L. 97-51, Section 133, Congress appropriated funds to be used in Fiscal Year 1982 for the cost of carrying out these close-out functions.

### Proposed Amendments

On March 11, 1982 there was published in the **Federal Register** (47 FR 10598) a notice of proposed rulemaking proposing to amend former Community Services Administration (CSA) rules governing continued expenditure of grant funds under "planned minimum number of months" grants and governing the time period allowed for submission of audits. These proposed amendments provided a definite termination date for all grants; they also reduced the annual audit period for grantees from 6 months to 60 days (90 days for public grantees) and the final audit period from 90 days to 60 days (unchanged for public grantees).

Interested parties were given until April 12, 1982 to submit comments. Fifteen comments were received; five addressed the conversion of planned minimum number of months grants to a definite termination date and twelve addressed the shortening of audit submission deadlines.

Although we have carefully evaluated the comments opposing the proposed rules or suggesting changes, we are adopting both rules as proposed, with the exception of one technical amendment to the termination date rule and the addition of provisions defining more clearly the circumstances under which grantees may receive an extension of the deadline for submission of audits.

The technical modification has been made to the provision stating when a planned minimum number of months grant will terminate. The purpose of this change is to make it clear that no such grant will terminate before June 24, 1982, except by exhaustion of the fund balance in the grant. A detailed discussion of the comments on these two proposed rules follows.

### Termination Dates

We are revising the regulations, as proposed, to establish a termination date for those CSA grants that do not presently specify a termination date for use of funds but instead indicate a planned minimum number of months for which funding was provided. Under the rule, the end of the planned minimum number of months becomes the termination date.

The most frequent suggestion in the five comments addressing the change was that grantees having planned minimum number of months grants be permitted to continue to expend funds until September 30, 1982, even if the planned minimum number of months expires before that date. Another comment advocated allowing grant expenditures until the end of the grantee's current program year, which would in some cases run well into Fiscal Year 1983. Arguments advanced for such extensions were that they would allow programs to be continued until the Fiscal Year 1983 block grant fundings are known, that they would allow grantees to follow the Federal Fiscal Year, that they would allow grantees to

operate on the basis of a date certain for the termination of their programs, and that grantees have already budgeted expenditures of funds past the new termination dates.

We do not believe that the revised rule unreasonably restricts grantees in carrying out their planned programs. No grant is terminated before its planned minimum number of months, and that is the time in which most of a grantee's funds were expected to be expended. Many grantees affected will have had more than their planned minimum of months already, since many of their grant periods end prior to the date on which this rule goes into effect.

The argument that grantees should be allowed to continue their programs until the Fiscal Year 1983 block grant funds become available, does not demonstrate the need for extension of current grants. Out of fifty-seven eligible states and territories, forty-seven are already administering the block grant; in these forty-seven states and territories, grantees are eligible for Fiscal Year 1982 block grant funds. In the other ten states, OCS is making transition grants which serve the same purposes. Thus the block grant grant program is essentially already in effect, and no purpose would be served by extending previous CSA grants pending developments under that program. On the contrary, the advanced status of the replacement block program supports the desirability of an early conclusion of the repealed CSA program.

The public purpose served by the imposition of an early, fixed termination date is the completion of closeout by September 30, 1982 for as many former CSA grants as possible and the attainment of the greatest possible progress by that date in closeout of those grants which cannot be completely closed out. Even with the shortened audit submission deadline discussed below, complete closeout of grants terminating in accordance with this rule requires perfect compliance with all deadlines on the part of the grantees and OCS. In the event costs are disallowed and an audit disallowance appeal filed, such grants cannot be completely closed out in Fiscal Year 1982, even under optimum conditions. For any grants extended to September 30, closeout cannot even be commenced until Fiscal Year 1983.

As only very limited funds have been budgeted for administration of CSA closeout in Fiscal Year 1983, and none have been appropriated, it is essential for OCS to complete as large a percentage of closeout activities in Fiscal Year 1982 as possible. Where closeout of a grant cannot be completed by September 30, it is the intention of OCS to complete as many stages of the closeout process as possible. For example, some grants may have only an audit disallowance appeal outstanding, other grants may have questioned costs outstanding but their audit in, while still other grants may be in the audit process but have all program activities completed.

The argument, made in one comment, that extending grants to September 30, 1982 would allow coordination with the Federal Fiscal Year and would create a fixed termination date is not persuasive. Most CSA grantees do not follow the Federal Fiscal Year; moreover, the rule does establish a fixed date for the conclusion of each grant.

Two comments requested the adoption of additional standards and procedures for the granting of extensions. As the effect of this rule is to place grantees with a planned minimum number of months grant on the same basis as grantees already having a termination date, existing procedures for requesting a no-cost extension will be used. Requests for such extensions should be addressed to the responsible program official; OCS will deal with them on a case-by-case basis.

One comment was based on a misinterpretation that the termination date will be retroactive. As noted above, the language has been altered to make it unmistakably clear that no new termination date will take effect until June 24, 1982. Furthermore, any extension of a grant period already allowed by CSA or OCS remains in effect and the new termination date in such extended grants will be the last day of the extension.

**Audit Submission Deadlines**

Most of the comments addressing this issue questioned the feasibility of submitting audits within the 60 day deadline and advocated a longer period, typically 90–120 days instead of 60 as proposed. Many commentators argued that the accounts could not be closed immediately upon the end of grant, so the auditors would in fact have only a few weeks to audit them. Furthermore, it was said that the draft audit has to be submitted to the grantee for corrections and comments before being finalized and transmitted to the Inspector General. The difficulty in getting all the information necessary to close the grantee's accounts was seen as the most substantial obstacle to compliance with a shortened audit submission deadline.

For the reasons discussed above in connection with the termination date rule, there is an essential public purpose in expediting closeout of former CSA grants so that as much of the closeout task as possible can be accomplished in Fiscal Year 1982. The receipt of audits is perhaps the most crucial factor in the pace of closeout. It has been and is the recommendation of the Inspector General that a 60 day audit period is a feasible and desirable way to meet the objective of making audits available in time to meet OCS closeout objectives.

OCS has carefully considered the argument that accounts cannot be closed soon enough to leave sufficient time for the auditor to review them. OCS believes, however, that the auditors can carry out many of the tasks comprising an audit before the grantee's accounts are completely closed. For example, all accounting systems review and most sampling procedures can be carried out before closing the books. Although some grantees may need to adopt unusual approaches or make special efforts, OCS believes that meeting the deadline is entirely feasible.

The alternative of a general 90 day audit deadline would result in the submission of many audits (and in particular those of the grants terminating on June 24, 1982 as a result of the new termination dates discussed above) too late to complete closeout of these grants by September 30.

Some comments also argued that it is unfair to allow public grantees 90 days to submit their audit while non-public grantees receive only 60. This differential was based on the conclusion of the Office of Management and Budget that the ordinary requirement of 90 days in which to submit these reports could be waived for non-public grantees but not for public grantees. Experience has shown that public grantees typically need more time to submit audit reports, than do non-public grantees.

There is a real need for a 60 day audit submission deadline which cannot be met by a general 90 day or longer deadline. As public grantees are only ten percent of all CSA Grantees, the allowance of 90 days for them does not seriously interfere with the attainment of the public purpose of expediting closeout. While aware of the difficulty of meeting this deadline, OCS finds it essential to the timely and expeditious closeout of CSA grant activities. Nevertheless, in light of the particular circumstances that may confront particular grantees, we are revising the regulations to permit an extension of time of up to 30 days when a non-public grantee makes a reasonable showing that, despite special effort, it cannot meet the 60 day deadline. Any longer extension for a private grantee or any extension for a public grantee will

require a showing of extraordinary circumstances.

One comment suggested that, where a grantee has more than one CSA grant, the audit should not be done until the termination of its last grant. We have not adopted this suggestion because it would excessively and unnecessarily delay closeout of those grants that are capable of being concluded at an early date.

**Regulatory Impact and Regulatory Flexibility Act**

These changes are intended to facilitate the orderly closeout of CSA grant activities in the most efficient and expedient way possible. Executive Order 12291, which requires the preparation of a regulatory impact analysis for regulations that have an annual effect on the national economy of $100 million or more, is not applicable to these amendments. They will have no appreciable effect on the national economy and do not constitute a "major rule" as defined in the Executive Order.

Neither do the provisions of the Regulatory Flexibility Act of 1980 (5 U.S.C. Ch. 6) apply to these amendments. That statute requires that for each rule with a "significant economic impact on a substantial number of small entities," an economic analysis must be prepared in an effort to anticipate and reduce the impact of rules and paperwork requirements on small businesses. These regulations will have no significant economic impact upon CSA grantees, but will merely facilitate the orderly close-out and final audit process necessary to carry out the congressionally mandated termination of CSA program acitivities. Accordingly, the Secretary hereby certifies that a regulatory flexibility analysis is not required.

**List of Subjects in 45 CFR Parts 1050, 1067, 1068**

Community action programs, Grant programs—social programs.

For the reasons set out in the preamble, Parts 1050, 1067, and 1068 of Chapter X, Subtitle B, Title 45 of the Code of Federal Regulations are amended as follows:

## PART 1050—UNIFORM FEDERAL STANDARDS

1. By revising the authority citation for Part 1050 as follows:

**Authority:** Sec. 602, 78 Stat. 530 (42 U.S.C. 2942); §§ 1050.112 and 1050.113 also issued under sec. 682(e), Pub. L. 97–35, 95 Stat. 519 (42 U.S.C. 9911).

2. By revising paragraph (c) of § 1050.112 to read as follows:

**§ 1050.112 Standards.**

* * * * *

(c) Within 60 calendar days after the completion of a grant, the grantee shall submit to the Office of Community Services (OCS) all financial, performance, and other reports required as conditions of the grant, except public grantees shall submit such required reports within 90 days of the grant's completion. (See references (7), (8), and (13) for procedures.) All audit reports must be addressed to the Office of the Inspector General, CSA/OCS, Department of Human Services, Room 548, 1200 19th Street, NW., Washington, D.C. 20506. All other required reports must be addressed to the Office of Community Services, Department of Health and Human Services, 1200 19th Street, NW., Washington, D.C. 20506. A grantee may request an extension of this deadline from the appropriate office. An extension of up to 30 days will be granted to a non-public grantee upon a showing of reasonable cause that the grantee, despite special efforts, cannot submit the required reports within 60 days. Further extensions for non-public grantees or any extensions for public grantees will be granted only in extraordinary circumstances.

3. By revising the introductory text of paragraph (b)(1)(i) of § 1050.113 to read as follows:

**§ 1050.113 CSA implementing policies and procedures.**

* * * * *

(b) * * * (1) *Scope of audit.*

(i) Within 60 days after the date of completion of a CSA grant, the grantee must submit a final audit of grant operations, except that the final audit for public grantees shall be submitted within 90 days after the grant's completion. Audit reports must be directed to the Office of the Inspector General, CSA/OCS, at the address specified in § 1050.112(c). Final audits shall be conducted in accordance with the Accounting System Survey and Audit Guide, CSA Manual 2410–1, except that the scope of the audit shall be adjusted as follows:

* * * * *

## PART 1067—FUNDING OF CSA GRANTEES

4. By revising the authority citation for part 1067 as follows:

**Authority:** Secs. 213, 602, 604 of the Economic Opportunity Act of 1964, as amended; 81 Stat. 395; 78 Stat. 528; 81 Stat. 715 (42 U.S.C. 2796, 2942, 2944); § 1067.30–3 also issued under sec. 682(e), Pub. L. 97–35, 95 Stat. 519 (42 U.S.C. 9911).

5. By revising paragraph (c) of § 1067.30–3, as follows:

**§ 1067.30–3 Purpose.**

This subpart provides for:

* * * * *

(c) Grantees' use of funds through the program account funding period. A grantee may not incur expenses under its program account after the termination date entered in column 12 of CSA Form 314, or after the expiration of the planned number of months for which funding is provided (column 13 of CSA Form 314). Except as provided in subparagraphs 1 and 2 of this paragraph, grant funds that are not expended by the end of the program account funding period must be returned to the Office of Community Services (OCS) in accordance with 45 CFR 1050.112(b).

(1) *Exception.* Under a grant with a planned minimum number of months which expires before June 24, 1982 funds may be used until June 24, 1982.

(2) *Extensions and reprogramming.* If a grantee applies for an extension of time in which to use the funds under its approved work program, OCS may extend the program account funding period under such terms and conditions as it deems appropriate. Alternatively, OCS may reprogram unexpended funds as part of a new grant action if the grantee is awarded an OCS grant pursuant to the block grant transition provisions of 42 U.S.C. 9911.

## PART 1068—GRANTEE FINANCIAL MANAGEMENT

6. By revising the authority citation for Subpart 1068.42 as follows:

**Authority:** Sec. 602, 78 Stat. 530 (42 U.S.C. 2942); § 1068. 42–8 also issued under sec. 682(e), Pub. L. 97–35, 95 Stat. 519 (42 U.S.C. 9911).

7. By adding new paragraph (a)(2) to § 1068.42–8 as follows:

**§ 1068–42–8 Required annual audit.**

(a) * * *

(2) *Audits for Periods Ending on or After October 1, 1981.* With respect to program years or grant periods ending on or after October 1, 1981, the grantee's auditor must submit five (5) copies of the audit report to the Office of the Inspector General, CSA/OCS, at the address specified in § 1050.112(c), within 60 days after the end of the audited program year or grant period, except that audit reports for public grantees shall be submitted within 90 days after the end of the audited period. A grantee may request an extension of this deadline from the appropriate office. An extension of up to 30 days will be

granted to a non-public grantee upon a showing of reasonable cause that the grantee, despite special efforts, cannot submit the audit report within 60 days. Further extensions for non-public grantees or any extensions for public grantees will be granted only in extraordinary circumstances.

* * * * *

Dated: April 28, 1982.

**Robert L. Trachtenberg,**

*Acting Director, Office of Community Services.*

Dated: May 7, 1982.

**Richard S. Schweiker,**

*Secretary of Health and Human Services.*

[FR Doc. 82-14119 Filed 5-24-82; 8:45 am]

BILLING CODE 8010-01-M

## FEDERAL COMMUNICATIONS COMMISSION

### 47 CFR Part 73

**[BC Docket No. 81-819; RM-3839]**

### FM Broadcast Station in Colorado Springs, Evergreen Lamar, Monte Vista, and Pueblo, Colorado; Changes made in Table of Assignments

**AGENCY:** Federal Communications Commission.

**ACTION:** Final rule.

**SUMMARY:** Action taken herein assigns FM Channel 243 to Evergreen, Colorado, and substitutes channels in four other Colorado communities to accommodate the change. Stations on two occupied channels are modified to specify operation on the newly assigned channels. The assignment would provide a first local aural service to Evergreen.

**DATE:** Effective July 19, 1982.

**ADDRESS:** Federal Communications Commisssion, Washington, D.C. 20554.

**FOR FURTHER INFORMATION CONTACT:** Nancy V. Joyner, Broadcast Bureau (202) 632-7792.

**SUPPLEMENTARY INFORMATION:**

**List of Subjects in 47 CFR Part 73**

Radio broadcasting.

**Report and Order (Proceeding Terminated)**

Adopted: May 11, 1982.

Released: May 17, 1982.

In the Matter of Amendment of § 73.202(b), Table of Assignments, FM Broadcast Stations. (Colorado Springs, Evergreen, Lamar, Monte Vista, and Pueblo, Colorado).

1. Before the Commission is the *Notice of Proposed Rule Making and Order to Show Cause* in this proceeding, 46 FR 59555, published December 7, 1981. In that document, the Commission proposed the assignment of Channel 243 to either Evergreen or Denver, Colorado, with channel substitutions at Colorado Springs, Lamar, Monte Vista, and Pueblo, Colorado. Additionally, the licensees of FM Stations KKFM, Colorado Springs, and KCCY, Pueblo, were ordered to show cause why their licenses should not be modified to specify operation on the newly assigned channels. Comments were received from Carolyn Gaspard and Penny Eilersen, d.b.a. Gaspard and Eilersen ("petitioners"), and from Jerry Rhoads ("Rhoads").[1] Reply comments were filed by Kennebec-Colorado Broadcasting Corporation ("Kennebec"), licensee of Station KCCY at Pueblo, Colorado.

2. In order to accommodate the proposed assignment of Channel 243 to either Evergreen or Denver, the following channel substitutions are required to conform with the minimum distance separation requirements of § 73.207 of the Commission's Rules: Channel 251 for Channel 243 (Station KKFM), Colorado Springs; Channel 245 for Channel 250 (Station KCCY), Pueblo; Channel 237A for vacant Channel 244A at Monte Vista; and Channel 289 for vacant Channel 245 at Lamar, Colorado.

3. In their proposal, petitioners stated that Evergreen is a mountain community, located within the foothills of Colorado's Front Range. Petitioners stated that although Evergreen is located within 15 miles of Denver, it has separate needs and interests apart from that community. According to petitioners the present means of providing information to the citizens of Evergreen is through two local newspapers that are published twice weekly. Petitioners further asserted that although Evergreen receives the signals of the Denver stations, they do not provide programming responsive to the local needs and interests of their community. For this reason, petitioners stressed the requirement for a first local outlet at Evergreen, with particular emphasis placed on the need to provide public safety information emanating from a combination of potentially hazardous occurrences in the area.

4. The *Notice* requested petitioners to provide a *Roanoke Rapids/Anamosa* study to justify their proposal to assign Class C Channel 243 to Evergreen, indicating the amount of first and second service that would be provided to surrounding areas and populations. *See, Roanoke Rapids, North Carolina,* 9 F.C.C. 2d 672 (1967); *Anamosa, Iowa,* 46 F.C.C. 2d 520 (1975). We indicated therein that absent such a showing, we would assume that no first or second service would be provided in view of the nine Denver Class C stations operating nearby. We also noted that this proposal would require a transmitter site restriction of 9.6 kilometers (6.0 miles) southeast of Evergreen to avoid short spacing to Station KSBT (FM) (Channel 244A), in Steamboat Springs, Colorado. Although a Class C channel would not normally be assigned to a community the size of Evergreen, petitioner demonstrated that there were no Class A channels available.

5. As pointed out in the *Notice,* the assignment of Channel 243 to Evergreen would cause preclusion to occur on Channels 242, 243 and 244A in seven communities which have a population in excess of 1,000 persons. Five of these communities have assignments,[2] and the remaining two have assignments available.[3]

6. As noted above, as an alternative to petitioners' Evergreen proposal, we proposed to assign Class C Channel 243 to the larger city of Denver, which could be applied for at Evergreen under the 15-mile rule (§ 73.203(b) of the Commission's Rules). This option was made consistent with prior Commission precedent where the community requested is not considered large enough to warrant a Class C assignment without a special showing of need, and the community is close enough to the larger city to fall within § 73.203(b). *See, Albuquerque and Alameda, New Mexico,* 48 R.R. 2d 1327 (1981); *Anchorage and Eagle River, Alaska,* 50 R.R. 2d 215 (1981). We proposed this option due to our concern that a high-powered Class C station allocated to Evergreen would inevitably seek to attract advertising from Denver and thereby serve the larger market. The *Notice* also reflected that a Class A could conceivably be assigned to Evergreen with less substitutions than the Class C proposal would entail. However, we did not propose a Class A channel since petitioner was not interested in such an assignment with the obligation to reimburse other stations for channel substitutions.

[1] In addition, a letter of support for the assignment of Channel 243 to either Evergreen or Denver, Colorado, was filed by Peter G. Motta. This letter was received too late to be considered as comments.

[2] The five communities and their assignments are: Sidney, Nebraska (Channel 237A); Kimball, Nebraska (Channel 261A); Brush, Colorado (Channel 296A); Aspen, Colorado (Channel 249A); and Wheatland, Wyoming (Channel 269A).

[3] The two communities are Gering, Nebraska, and Holyoke, Colorado. Petitioner advised that Channel 244A is available for assignment to either community.

7. Evergreen (population 6,393),[4] in Jefferson County (population 371,741), is located approximately 24 kilometers (15 miles) southwest of Denver. It presently is devoid of local service.

8. Denver (population 491,396) is presently assigned nine FM channels, and could be assigned an additional allocation pursuant to the Commission's population guidelines. This option would also require the two permittees (Stations KKFM, Colorado Springs, and KCCY, Pueblo), to change frequencies to accommodate the proposal.

9. Petitioners' comments, while advocating support of the assignment to Evergreen, stated that due to supervening circumstances, they could not commit themselves to apply for the channel, if assigned. However, the comments filed by Jerry Rhoads expressed his interest in the proposal to assign Channel 243 to Evergreen (Option I), and expressed his determination to apply for the channel, if assigned. In a supplemental comment, Rhoads also asserted his willingness to reimburse Stations KKFM, Colorado Springs, and KCCY, Pueblo, for the reasonable costs incurred in switching frequencies to accommodate the proposal.

10. Also, in response to our request in the *Notice* to provide *Roanoke Rapids/Anamosa* data, Rhoads submitted an engineering study which indicates that no first or second service would be provided by the proposed assignment of Channel 243 to Evergreen, due to its close proximity to the Class C stations operating in Denver.

11. In reply comments, Kennebec states that it does not oppose the frequency change of its Station KCCY, provided reimbursement is made and the switch is effectuated as rapidly as possible to enable it to actively promote its new dial location. In this regard, Kennebec notes that it has expended large sums to advertise and establish its identity on Channel 250. However, in view of the proposed modification directive, it states that it could neither afford to continue advertising the frequency it must ultimately vacate, nor could it afford not to.

**Conclusions**

12. As a preliminary matter, we have received no expression of interest in the possibility of a Class A assignment to Evergreen. Thus, we have decided not to pursue that option. A showing of first and second FM service is generally an important prerequisite to assigning a Class C channel to smaller communities. *See, e.g., Cobleskill, New York,* 48 R.R. 2d 1406 (1981). Here, no first or second service would be provided as a result of Evergreen's proximity to Denver, which has nine FM stations. However, the Class C allocation will satisfy one of the Commission's assignment priorities [5] by providing Evergreen with its first local broadcast service. *See Freeport, Texas,* 45 FR 21638, published April 2, 1980.

13. Kennebec voiced its concern earlier that the proposal to add Class C Channel 243 to Evergreen was merely an effort to add another station to Denver. However, we find no evidence in the record of this proceeding of an intention to serve the larger community of Denver. Rather, it appears that the intention of Rhoads is truly to serve Evergreen. In fact, because the transmitter site will be restricted to an area (approximately 20 miles south) located away from Denver, such a station would be at a substantial disadvantage against other Denver stations. We believe that this substantial distance from Denver distinguishes this case from others in which we have chosen the larger city for assignment. In *Albuquerque, New Mexico, supra,* the distance involved was 7 miles. In the *Anchorage, Alaska,* case *supra,* the suburban community was approximately 13 miles away with several Class A channels available. Although no first or second service would be offered here, the proposed station could cover sparsely populated areas not now covered by the Denver stations.

14. The preclusive impact of the proposed assignment to Evergreen is insignificant since it has been demonstrated that channels are either assigned to the precluded communities, or available thereto in the event an interest should develop in the future. Thus, we do not find that preclusion is substantial enough to bar a grant of the proposal.

15. One final matter to be resolved involves Kennebec's request to proceed with its change of frequencies for Station KCCY from Channel 250 to Channel 245 prior to the selection of the eventual permittee at Evergreen. This proposal cannot be accommodated unless Station KKFM (Channel 243) at Colorado Springs is willing to change frequencies to Channel 251 simultaneously with Station KCCY's changeover.[6] Section 73.207 of the Commission's Rules requires a minimum distance separation of 65 miles between second adjacent Class C facilities, whereas the distance between Pueblo and Colorado Springs is 29 miles. As is our general policy, Station KKFM is not required to change frequencies until a permit is issued for Channel 243 at Evergreen, Colorado. Of course, it may do so sooner if it wishes.

16. In view of the above, we have determined that the public interest would be served by assigning Channel 243 to Evergreen, as proposed in Option I of the Notice. Persuasive information was submitted regarding the desirability of making an FM assignment to that community, which could also render a first local aural service.

17. Accordingly, pursuant to authority contained in §§ 4(i), 5(d)(1), 303(g) and (r) and 307(b) of the Communications Act of 1934, as amended, and §§ 0.204(b) and 0.281 of the Commission's Rules, it is ordered, That effective July 19, 1982, and the FM Table of Assignments, § 73.202(b) of the Commission's Rules, is amended as follows:

| City | Channel No. |
|---|---|
| Colorado Springs, Colorado | 251 |
| Evergreen, Colorado | 243 |
| Lamar, Colorado | 277, 288 |
| Monte Vista, Colorado | 237A |
| Pueblo, Colorado | 245 |

18. It is further ordered, pursuant to the authority contained in § 316(a) of the Communications Act of 1934, as amended, That the outstanding license for Station KKFM, held by Ski-Hi, Inc. at Colorado Springs, Colorado, is modified effective July 19, 1982, to specify operation on Channel 251, in lieu of Channel 243, with the condition that it will be reimbursed for the reasonable costs incurred in switching frequencies from the ultimate permittee of Channel 243, Evergreen. Ski-Hi, Inc. shall inform the Commission in writing by no later than (————?————), 1982, of its consent to this modification. Station KKFM may continue to operate on Channel 243 unitl a permit is issued for Channel 243 at Evergreen or until its license renewal expiration date of April 1, 1983, whichever is first. Additionally, the license modification for Station KKFM is subject to the following conditions:

(a) The licensee shall file with the Commission a minor change application for a construction permit (Form 301), specifying the new facilities.

[4] This population figure was supplied by petitioner since Evergreen is an unincorporated community and thus not listed in the preliminary 1980 U.S. Census. However, all other population figures are derived from the 1980 U.S. Census, Advance Reports, unless otherwise indicated.

[5] *See, Further Notice of Proposed Rule Making,* 27 FR 7797–98, published August 7, 1967; *Anamosa and Iowa City, Iowa,* 46 F.C.C. 2d 520 (1970).

[6] Ski-Hi, Inc., licensee of Station KKFM (Channel 243) did not respond to the *Order to show Cause* and is therefore deemed to consent to the modification as proposed therein.

(b) Upon grant of the construction permit, program tests may be conducted in accordance with § 73.1620.

(c) Nothing contained herein shall be construed to authorize a major change in transmitter location or to avoid the necessity of filing an environmental impact statement pursuant to § 1.1301 of the Commission's Rules.

19. It is further ordered, pursuant to the authority contained in §316(a) of the Communications Act of 1934, as amended, That the outstanding license of Keenebec-Colorado Broadcasting Corporation for Station KCCY, Pueblo, Colorado, is modified effective July 19, 1982, to specify operation on Channel 245 in lieu of Channel 250, with the condition that it will be reimbursed for the reasonable costs incurred in switching frequencies from the ultimate permittee of Channel 243, Evergreen. The license modification for Station KCCY is subject to the following conditions:

(a) The licensee shall file with the Commission a minor change application for a construction permit (Form 301), specifying the new facilities.

(b) Upon grant of the construction permit, program tests may be conducted in accordance with § 73.1620.

(c) Nothing contained herein shall be construed to authorize a major change in transmitter location or to avoid the necessity of filing an environmental impact statement pursuant to § 1.1301 of the Commission's Rules.

20. It is further ordered, that the Secretary of the Commission shall send a copy of this Order by certified mail, return receipt requested, to Sky-Hi, Inc., Radio Station KKFM-FM, 225 South Academy Boulevard, Colorado Springs, Colorado 80910, and to Kennebec-Colorado Broadcasting Corporation, Radio Station KCCY-FM, c/o 315-8th Street, Pueblo, Colorado 81003.

21. It is further ordered, that this proceeding is terminated.

22. For further information concerning the above, contact Nancy V. Joyner, Broadcast Bureau, (202) 632-7792.

(Secs. 4, 303, 48 stat., as amended, 1066, 1082; 47 U.S.C. 154, 303).

Federal Communications Commission.

**Roderick K. Porter,**

*Chief, Policy and Rules Division, Broadcast Bureau.*

[FR Doc 82-19184 Filed 5-24-82; 8:45 am]

BILLING CODE 6712-01-M

## 50 CFR Part 80

## Federal Aid in Fish and Wildlife Restoration

**AGENCY:** Fish and Wildlife Service, Interior.

**ACTION:** Final rule.

**SUMMARY:** This rule amends current requirements for participation by State fish and wildlife agencies in the Federal Aid in Wildlife Restoration program and the Federal Aid in Fish Restoration program. The amendments simplify existing language, clarify requirements, and delete certain sections which are no longer applicable or are adequately covered in other regulations and policies such as OMB Circular A-102.

**EFFECTIVE DATE:** This rule is effective June 24, 1982. Regional directors may defer implementation upon requests by grantees if the revised rule(s) would place an undue burden on such grantees. However, final implementation may not exceed December 31, 1982.

**FOR FURTHER INFORMATION CONTACT:** Charles K. Phenicie, Chief, Division of Federal Aid, U.S. Fish and Wildlife Service, Washington, D.C. 20240, telephone 703/235-1526.

**SUPPLEMENTARY INFORMATION:** Proposed rulemaking was published on pages 57471-57474 of the **Federal Register** of August 28, 1980, and invited comments for 45 days ending October 14, 1980. A correction was published on page 59914 of the **Federal Register** of September 11, 1980, and the comment period extended to October 31. Comments were received from 28 sources including individuals, organizations, and State fish and wildlife agencies. The following is a summary of the major comments received and our response to each.

1. *Comment.* Several commenters stated that the groups of fish and/or wildlife species eligible for funding were too restricted and suggested broadening to include a wider range of species.

*Response.* The Acts and the legislative history support our interpretation that the intent of the programs should be limited to those groups of species as stated. Under the Wildlife Restoration program, the only limit on species is wild birds and mammals. One purpose of these rules was to make clear that wild birds and mammals were not restricted to hunted species. The Fish Restoration Act is specific in addressing "fish of material value for sport or recreation." We feel that the term fish is used in its normal sense as meaning fin fish.

2. *Comment.* One commenter objected to our wording changes which eliminated hunting and fishing from project purposes.

*Response.* There was no intent to imply that hunting and fishing were not legitimate purposes or results to be accomplished. These are included in the public uses of fish and wildlife resources.

3. *Comment.* One commenter stated that the rules should be revised to include Indian tribal governments as eligible participants.

*Response.* The Acts are specific in defining State fish and wildlife agencies as participants, including provisions for the allocation of funds to these agencies. The basic Acts would need to be amended before we could change the participant eligibility.

4. *Comment.* One commenter suggested a revision to § 80.4, Diversion of license fees, to clarify that the use of revenues from hunting and fishing license fees are restricted to only those functions of a State fish and wildlife agency which are related to its sport fish and wildlife management responsibilities.

*Response.* We agree with the suggestion to distinguish fish and wildlife agencies and their functions when such agencies are a part of a larger unit of State government. However, we do not agree with the need to further constrain the use of license revenues to sport fish management functions. Such a restriction would impose an unnecessary burden on all States without a clear indication of a problem requiring treatment.

5. *Comment.* One commenter stated that the purpose of hunter education projects, as written, does not accurately reflect the full range of project purposes.

*Response.* We agree with this comment and have revised § 80.5(2) to emphasize the broader purpose of the hunter education program.

6. *Comment.* One commenter suggested the inclusion of instruction in trapping as eligible under the hunter education program.

*Response.* The eligible project purpose as stated for the hunter education program does not exclude training related to trapping when it is an intregal part of the State's hunter education project. Such training is not, in itself, a distinct project purpose requiring treatment in these rules.

7. *Comment.* Several commenters stated that the revision of Section 80.9, Notice of desire to participate, is not clear on the process required for making such notices.

*Response.* Section 5 of both Acts requires that any State desiring to participate shall notify the Secretary to

this effect within 60 days after receiving the annual certificate of apportioned funds. We have required this notification of derise following the preliminary apportionment of funds. The purpose of § 80.9 is to provide two options for the States to meet the requirement of the Acts. One option is to send a letter expressing the desire to participate. The second option recognizes that a State has expressed its desire when the regional director has received or has on file, during the 60-day period, a properly executed Application for Federal Assistance. If the Application contains plans for the use of the funds apportioned, then the requirement is met.

8. *Comment.* Several commenters stated that the term "significant net revenue" as a condition for determining paid license holders in not clear.

*Response.* We agreed that "significant" to qualify net revenue is not necessary and confusing since the term "net revenue" is further explained. We plan to develop additional guidance on this matter to aid the States in making determinations of net revenue.

9. *Comment.* Several commenters suggested that the rules on determining paid license holders should specifically address lifetime licenses, since such licenses are common among the States.

*Response.* We agree that the counting of lifetime hunting and fishing licenses for license certification purposes should be covered by these rules. Section 80.10(c) is revised to provide criteria for counting licenses valid for more than one year, including lifetime licenses.

10. *Comment.* One commenter stated that the criteria of a substantial project related to cost and benefits are subject to considerable interpretation.

*Response.* We agree that these criteria are judgmental; however, the statement of principle is sound when taken in the context of basic project requirements. The rule cannot substitute for reasonable judgments, nor is it intended to require complex quantitative computations.

11. *Comment.* One commenter suggested a revision in § 80.14 to specify the treatment of proceeds from the sale of property no longer needed or useful for the purposes for which it was acquired.

*Response.* The intent of this section is to provide basic requirements rather than the procedures. Those procedures suggested are adequately covered in Attachment N of OMB Circular A-102 and the Federal Aid Manual. We have revised § 80.14(3) to reference Attachment N of Circular A-102 rather than to repeat its basic provisions in the rule.

12. *Comment.* One commenter suggested a revision to § 80.17 to clearly state that the costs for maintenance of capital improvements acquired or constructed under the programs are approvable.

*Response.* We agree with this comment and have revised § 80.17 to incorporate the suggestion.

In addition to changes made as a result of comments received and some editorial changes, we considered a recommendation by the Assistant Solicitor for Fish and Wildlife to clarify that the prohibition against the diversion of capital assets acquired with license fees also includes income derived from such assets. This recommendation was adopted and § 80.4(a)(2) was revised to incorporate the suggested provision. The effect of this change is to prohibit the diversion of income from capital assets in addition to those assets derived from hunting and fishing license revenues.

On December 24, 1980, Pub. L. 96-597 was enacted. Sections 302(a) and 302(b) of that Act amend Section 8(a) of the Federal Aid in Wildlife Restoration Act, 16 U.S.C. 669g-1, and Section 12 of the Federal Aid in Fish Restoration and Management Projects Act, 16 U.S.C. 777k, respectively, to provide for participation in the Federal Aid programs by the Commonwealth of the Northern Mariana Islands. Accordingly, changes have been made in §§ 80.1(b), 80.2, and 80.12 to include the Commonwealth of the Northern Mariana Islands. Because the amendments to the Federal Aid statutes became effective after the beginning of Fiscal Year 1981, the Commonwealth of the Northern Mariana Islands will receive its apportionment and participate in the Federal Aid program commencing with Fiscal Year 1982 which begins on October 1, 1981.

The Federal Aid in Fish Restoration and Federal Aid in Wildlife Restoration programs are included in the *Catalog of Federal Domestic Assistance* under numbers 15.605 and 15.611.

The principal author of this proposal is Robert N. Bartel, U.S. Fish and Wildlife Service, Division of Federal Aid, Washington, D.C. 20240, telephone 703/235-1526.

Note.—The Department of the Interior has determined that this document is not a major rule and does not require a regulatory impact analysis under Executive Order 12291, nor does the rule have a significant economic effect on a substantial number of small entities under the Regulatory Flexibility Act.

**Information Collection:**

The information collection requirements contained in this rule have been approved by the Office of Management and Budget under 44 U.S.C. 3507 and assigned clearance numbers 1018-0007 and 1018-0048.

**List of subjects in 50 CFR 80**

Fish, Grant programs-natural resources, Grant administration-wildlife.

Part 80 of Title 50, Code of Federal Regulations, in revised as set forth below.

## PART 80— ADMINISTRATIVE REQUIREMENTS, FEDERAL AID IN FISH AND FEDERAL AID IN WILDLIFE RESTORATION ACTS

Sec.



Authority: Federal Aid in Fish Restoration Act (16 U.S.C. 777i) and Federal Aid in Wildlife Act (16 U.S.C. 669i).

Note.—The information collection requirements contained in this rule have been approved by the Office of Management and Budget under 44 U.S.C. 3507 and assigned clearance number 1018-0048, except for § 80.10 which is assigned clearance number 1018-0007.

### § 80.1 Definitions.

As used in this part, terms shall have the following meanings:

(a) *The Federal Aid Acts or the Acts.* The Federal Aid in Wildlife Restoration Act of September 2, 1937, as amended (50 Stat. 917; 16 U.S.C. 669-669i), and the Federal Aid in Sport Fish Restoration Act of August 9, 1950, as amended (64 Stat. 430; 16 U.S.C. 777-777k).

(b) *State.* Any State of the United States; the territorial areas of Guam, the Virgin Islands, and American Samoa; the Commonwealth of Puerto Rico and the Commonwealth of the Northern Mariana Islands.

(c) *State fish and wildlife agency.* The agency or official of a State designated under State law or regulation to carry out the laws of the State in relation to the management of fish and wildlife

resources of the State. Such an agency or official which is also designated to exercise collateral responsibilities, e.g., State Department of Natural Resources, shall be considered the State fish and wildlife agency only when exercising the responsibilities specific to the management of the fish and wildlife resources of the State.

(d) *Secretary.* The Secretary of the Interior or his designated representative.

(e) *Director.* The Director of the U.S. Fish and Wildlife Service, or his designated representative. The Director serves as the Secretary's representative in matters relating to the administration and execution of the Federal Aid Acts.

(f) *Regional Director.* The Regional director of the U.S. Fish and Wildlife Service, or hs designated representative.

(g) *Federal Aid Manual.* The publication of the U.S. Fish and Wildlife Service which contains policies, standards and procedures required for participation in the benefits of the Acts.

(h) *Project.* A program of related undertakings necessary to fulfill a defined need which is consistent with the purposes of the Act.

(i) *Comprehensive fish and wildlife management plan.* A document describing the State's plan for meeting the long-range needs of the public for fish and wildlife resources, and the system for managing the plan.

(j) *Federal Aid Funds.* Funds provided under Federal Aid Acts.

**§ 80.2 Eligibility.**

Participation in the benefits of the Acts is limited to State fish and wildlife agencies as specified below:

(a) Federal Aid in Sport Fish Restoration—Each of the 50 States, the Commonwealth of Puerto Rico, the Comonwealth of the Northern Mariana Islands, Guam, the Virgin Islands, and American Samoa.

(b) Federal Aid in Wildlife Restoration—Each of the 50 States, the Commonwealth of Puerto Rico, the Commonwealth of the Northern Mariana Islands, Guam, and the Virgin Islands; except that the benefits afforded by Section 4(b) of the Act relating to hunter education projects are limited to the 50 States.

**§ 80.3 Assent legislation.**

A State may participate in the benefits of the Act(s) only after it has passed legislation which assents to the provisions of the Acts and has passed laws for the conservation of fish and wildlife including a prohibition against the diversion of license fees paid by hunters and sport fishermen to purposes other than administration of the fish and wildlife agency. Subsequent legislation which amends these state laws shall be subject to review by the Secretary. If the legislation is found contrary to the assent provisions, the State shall become ineligible.

**§ 80.4 Diversion of license fees.**

Revenues from fees paid by hunters and sports fishermen shall not be diverted to purposes other than administration of the State fish and wildlife agency. Administration of the State fish and wildlife agency includes only those functions of such an organization in exercising its authorities and responsibilities to manage the fish and wildlife resources of the State.

(a) A diversion of license fees occurs when a State fish and wildlife agency, through legislation or otherwise:

(1) Loses control of the expenditure of any portion of its license revenues, or

(2) Loses control of capital assets (or income therefrom) derived from license revenues, or

(3) Expends license revenues for any purpose other than administration of the State fish and wildlife agency.

(b) If a diversion of license fees occurs, the State becomes ineligible to participate under the pertinent Act from the date the diversion is declared by the Director until:

(1) Control of expenditure or assets is returned, and

(2) An amount equal to license revenues or the current market value of assets diverted is returned.

(c) Federal funds obligated for projects approved prior to the date a diversion is declared remain available for expenditure on such projects without regard to the intervening period of the State's ineligibility.

**§ 80.5 Eligible undertakings.**

The following are eligible for funding under the Acts:

(a) Federal Aid in Wildlife Restoration Act.

(1) Projects having as their purpose the restoration, conservation, management, and enhancement of wild birds and wild mammals, and the provision for public use of and benefits from these resources.

(2) Projects having as their purpose the education of hunters and archers in the skills, knowledges, and attitudes necessary to be a responsible hunter or archer.

(b) Federal Aid in Sport Fish Restoration Act.

Projects having as their purpose the restoration, conservation, management, and enhancement of sport fish, and the provision for public use and benefits from these resources. Sport fish are limited to aquatic, gill-breathing, vertebrate animals, bearing paired fins, and having material value for sport or recreation.

**§ 80.6 Prohibited activities.**

The following are not eligible for funding under the Acts, except when necessary for the accomplishment of project purposes as approved by the regional director.

(a) Law enforcement activities conducted by the State to enforce the fish and game regulations.

(b) Public relations activities conducted to promote the State fish and wildlife agency.

**§ 80.7 Appeals.**

Any difference of opinion over the eligibility of proposed activities or differences arising over the conduct of work may be appealed to the Director. Final determination rests with the Secretary.

**§ 80.8 Availability of funds.**

Funds are available to a State for obligation or expenditure during the fiscal year for which they are apportioned and until the close of the succeeding fiscal year. For the purpose of this section, obligation of apportioned funds occurs when a project agreement is signed by the regional director.

**§ 80.9 Notice of desire to participate.**

Any State fish and wildlife agency desiring to avail itself of the benefits of the Acts shall notify the Secretary within 60 days after it has received a certificate of apportionment of funds available to the State. Notification to the Secretary may be accomplished by either of the following methods. In either method, the document must be signed by a State official authorized to commit the State to participation under the Act(s).

(a) Submitting to the regional director within the 60-day period a letter stating the desire of the State to participate in the Act(s); or,

(b) Having an approved Application for Federal Assistance which contains plans for the use of Federal Aid funds during the period of the apportionment.

**§ 80.10 Hunting and fishing license certification (OMB approval number 1018-0007 under 44 U.S.C. 3507).**

(a) Information concerning the number of persons holding paid licenses to hunt and the number of persons holding paid licenses to fish for sport or recreation in the State in the preceding year shall be furnished upon request of the Director by the fish and wildlife agency of each State on forms furnished by the Fish and Wildlife Service.

(b) This information shall be certified as accurate by the director of the State fish and wildlife agency. When requested by the Director, evidence used in determining accuracy of the certification shall also be furnished.

(c) License holders shall be counted over a period of 12 months; the calendar year, fiscal year, or other licensing period may be used provided it is consistent from year to year in each State. In determining licenses which are eligible for inclusion, the following guidelines shall be observed.

(1) Trapping licenses, commercial licenses, and other licenses which are not for the express purpose of permitting the holder to hunt or fish for sport or recreation shall not be included.

(2) Licenses which do not return net revenue to the State shall not be included. To qualify as a paid license, the fee must produce revenue for the State. Net revenue is any amount returned to the State after deducting agent or sellers fees and the cost for printing, distribution, control or other costs directly associated with the issuance of each license.

(3) Licenses valid for more than one year, either a specific or indeterminate number of years, may be counted in each of the years for which they are valid; provided that:

(i) The net revenue from each license is commensurate with the period for which hunting or fishing privileges are granted, and

(ii) Sampling or other techniques are used to determine whether the licensee remains a license holder in the year of certification.

(4) Combination fishing and hunting licenses (a single license which permits the holder both to hunt and fish) shall be included in the determination of both the number of paid hunting license holders and the number of persons holding paid licenses to fish for sport or recreation.

(5) Some licensing systems require or permit an individual to hold more than one license to hunt or to fish in a State. Such an individual shall not be counted more than once as a hunting or fishing license holder. The State fish and wildlife director, in certifying license information to the Director, is responsible for eliminating duplication or multiple counting of single individuals in the figures which he certifies. Sampling and other statistical techniques may be utilized by the certifying officer for this purpose.

### § 80.11 Submission of proposals.

A State may make application for use of funds apportioned under the Acts by submitting to the regional director either a comprehensive fish and wildlife management plan or project proposal.

(a) Each application shall contain such information as the regional director may require to determine if the proposed activities are in accordance with Acts, the provisions of this part, and the standards contained in the Federal Aid Manual.

(b) Each application and amendments of scope shall be submitted to the State Clearinghouse as required by Office of Management and Budget (OMB) Circular A-95 and by State Clearinghouse requirements.

(c) Applications must be signed by the director of the State fish and wildlife agency or the official(s) delegated to exercise the authority and responsibilities of the State's director in committing the State to participation under the Acts. The director of each State fish and wildlife agency shall notify the regional director, in writing, of the official(s) authorized to sign Federal Aid documents, and any changes in such authorizations.

### § 80.12 Cost sharing.

Federal participation is limited to 75 percent of eligible costs incurred in the completion of approved work or the Federal share specified in the project agreement, whichever is less, except that the non-Federal cost sharing for the Commonwealth of Puerto Rico, the Commonwealth of the Northern Mariana Islands, Guam, the Virgin Islands, and American Samoa shall not exceed 25 percent and may be waived at the discretion of the regional director.

(a) A minimum Federal participation of 10 percent of the estimated costs is required as a condition of approval.

(b) The non-Federal share of project costs may be in the form of cash or in-kind contributions. The allowability and evaluation of in-kind contributions are subject to the policies and standards prescribed in Office of Management and Budget (OMB) Circular A-102.

(c) The non-Federal share of project costs may not be derived from other Federal funds, except as authorized by specific legislation.

### § 80.13 Substantiality in character and design.

All projects proposed for funding under the Acts must be substantial in character and design. A substantial project (for fish and wildlife purposes) is one which:

(a) Identifies and describes a need within the purposes of the relevant Act to be utilized;

(b) Identifies the objectives to be accomplished based on the stated need;

(c) Utilizes accepted fish and wildlife conservation and management principles, sound design, and appropriate procedures; and

(d) Will yield benefits which are pertinent to the identified need at a level commensurate with project costs.

### § 80.14 Application of Federal aid funds.

(a) Federal Aid funds shall be applied only to activities or purposes approved by the regional director. If otherwise applied, such funds must be replaced or the State becomes ineligible to participate.

(b) Real property acquired or constructed with Federal Aid funds must continue to serve the purpose for which acquired or constructed.

(1) When such property passes from management control of the fish and wildlife agency, the control must be fully restored to the State fish and wildlife agency or the real property must be replaced using non-Federal Aid funds. Replacement property must be of equal value at current market prices and with equal benefits as the original property. The State may have a reasonable time, up to three years from the date of notification by the regional director, to acquire replacement property before becoming ineligible.

(2) When such property is used for purposes which interfere with the accomplishment of approved purposes, the violating activities must cease and any adverse effects resulting must be remedied.

(3) When such property is no longer needed or useful for its original purpose, and with prior approval of the regional director, the property shall be used or disposed of as provided by Attachment N of OMB Circular A-102.

(c) Federal Aid funds shall not be used for the purpose of producing income. However, income producing activities incidental to accomplishment of approved purposes are allowable. Income derived from such activities shall be accounted for in the project records and disposed of as directed by the Director.

### § 80.15 Allowable costs.

Allowable costs are limited to those which are necessary and reasonable for accomplishment of approved project purposes, and are in accordance with the cost principles of OMB Circular A-87.

(a) All costs must be supported by source documents or other records as necessary to substantiate the application of funds. Such documentation and records are subject

to review by the Secretary to determine the allowability of costs.

(b) Costs incurred prior to the effective date of the project agreement are allowable only when specifically provided for in project agreement.

(c) Projects or facilities designed to include purposes other than those eligible under the pertinent Act shall provide for the allocation of costs among the various purposes. The method used to allocate costs shall produce an equitable distribution of costs based on the relative uses or benefits provided.

(d) Administrative costs in the form of overhead or indirect costs for State central services outside of the State fish and wildlife agency must be in accord with an approved cost allocation plan and shall not exceed in any one fiscal year three percentum of the annual apportionment.

**§ 80.16 Federal aid payments.**

Payments shall be made for the Federal share of allowable costs incurred by the State in accomplishing approved projects.

(a) Requests for payments shall be submitted on forms furnished by the regional director.

(b) Payments shall be made only to the office or official designated by the State fish and wildlife agency and authorized under the laws of the State to receive public funds for the State.

(c) All payments are subject to final determination of allowability based on audit. Any overpayments made to the State shall be recovered as directed by the region director.

(d) The regional director may withhold payments pending receipt of all required reports or documentation for the project.

**§ 80.17 Maintenance.**

The state is responsible for maintenance of all capital improvements acquired or constructed with Federal Aid funds throughout the useful life of each improvement. Costs for such maintenance are allowable when provided for in approved projects. The maintenance of improvements acquired or constructed with non-Federal Aid funds are allowable costs when such improvements are necessary to accomplishment of project purposes as approved by the regional director, and when such costs are otherwise allowable by law.

**§ 80.18 Responsibilities.**

In the conduct of activities funded under the Acts, the State is responsible for:

(a) The supervision of each project to assure it is conducted as provided in the project documents, including:

(1) Proper and effective use of funds.

(2) Maintenance of project records.

(3) Timely submission of reports.

(4) Regular inspection and monitoring of work in progress.

(b) The selection and supervision of project personnel to assure that:

(1) Adequate and competent personnel are available to carry the project through to a satisfactory and timely completion.

(2) Project personnel perform the work to ensure that time schedules are met, projected work units are accomplished, other performance objectives are being achieved, and reports are submitted as required.

(c) The accountability and control of all assets to assure that they serve the purpose for which acquired throughout their useful life.

(d) The compliance with all applicable Federal, State, and local laws.

(e) The settlement and satisfaction of all contractual and administrative issues arising out of procurement entered into.

**§ 80.19 Records.**

The State shall maintain current and complete financial, property and procurement records in accordance with requirements contained in the Federal Aid Manual and OMB Circular A-102.

(a) Financial, supporting documents, and all other records pertinent to a project shall be retained for a period of three years after submission of the final expenditure report on the project. If any litigation, claim, or audit was started before the expiration of the three-year period, the records shall be retained until the resolution is completed. Records for nonexpendable property shall be retained for a period of three years following final disposition of the property.

(b) The Secretary and the Comptroller General of the United States, or any of their duly authorized representatives, shall have access to any pertinent books, documents, papers and records of the State.

**§ 80.20 Land control.**

The State must control lands or waters on which capital improvements are made with Federal Aid funds. Controls may be exercised through fee title, lease, easement, or agreement. Control must be adequate for protection, maintenance, and use of the improvement throughout its useful life.

**§ 80.21 Assurances.**

The State must agree to and certify that it will comply with all applicable Federal laws, regulations, and requirements as they relate to the application, acceptance, and use of Federal funds under the Acts. The Secretary shall have the right to review or inspect for compliance at any time. Upon determination of noncompliance, the Secretary may terminate or suspend those projects in noncompliance, or may declare the State ineligible for further participation in program benefits until compliance is achieved.

Dated: June 12, 1981.

**G. Ray Arnett,**

*Assistant Secretary for Fish and Wildlife and Parks.*

[FR Doc. 82-14203 Filed 5-24-82; 8:45 am]

BILLING CODE 4310-55-M

## DEPARTMENT OF COMMERCE

### National Oceanic and Atmospheric Administration

### 50 CFR Part 658

### Shrimp Fishery of the Gulf of Mexico

**AGENCY:** National Oceanic and Atmospheric Administration (NOAA), Commerce.

**ACTION:** Notice of closure.

**SUMMARY:** NOAA issues this notice adjusting the beginning date from June 1 to May 25 for closure of the fishery conservation zone off Texas to trawl fishing for all species except royal red shrimp. This area will remain closed through July 14. The management action is prescribed by existing regulations. The intended effect of this action is to allow harvest of brown shrimp at optimal commercial size.

**EFFECTIVE DATE:** Closure effective from 30 minutes after sunset on May 25, 1982, to 30 minutes after sunset on July 14, 1982. Public notice has been issued at least 72 hours prior to closure.

**FOR FURTHER INFORMATION CONTACT:** Jack T. Brawner, Acting Regional Director, 813-893-3141.

**SUPPLEMENTARY INFORMATION:** The Fishery Management Plan for the Shrimp Fishery of the Gulf of Mexico (FMP) provides for adjustments to the closing and opening dates for the seasonal closure of the fishery conservation zone (FCZ) off Texas. Implementing rules at 50 CFR 658.24 describe the Texas closure and specify that these adjustments be made by the Regional Director under criteria set out in that section.

Available information and estimates indicate an early closure is warranted and desirable. Biological data collected

by the Texas Parks and Wildlife Department on the size of shrimp indicate an earlier-than-usual movement of brown shrimp from the bays into the Gulf. The regulations state that the closure date must be based on a prediction of when the average size of brown shrimp leaving the bays to enter the Gulf will be 80 to 90 mm, on the strength of outgoing tides at that time, and on other ecological data. Most movement of shrimp from the bays takes place during periods of larger-than-average tidal duration, which this year occurs May 25 to 29. It is predicted that the average size of shrimp entering the Gulf of Mexico will be 90 mm on or about May 23, 1982. Based on this information, the Regional Director has determined that the customary closure dates of June 1 to July 15 will be changed to May 25 to July 14. The State of Texas will close its waters during these same days.

All trawling is prohibited between May 25 to July 14 in the area described in § 658.24(a), except that vessels may trawl for royal red shrimp beyond the 100-fathom depth contour. These vessels need no special permit or letter of authorization.

This action is taken under the authority of 50 CFR 658.24, and is taken in compliance with Executive Order 12291. (16 U.S.C. 1801 *et. seq.*)

**List of Subjects in 50 CFR Part 658**

Fish, Fisheries.

Dated: May 19, 1982.

**Robert K. Crowell,**

*Deputy Executive Director, National Marine Fisheries Service.*

[FR Doc 82-14218 Filed 5-24-82; 8:45 am]

BILLING CODE 3510-22-M

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

## Food and Drug Administration

## 21 CFR Part 444

**[Docket No. 80N-0187; DESI 8674]**

## Neomycin Sulfate-Sodium Propionate Otic Solution; Termination of Stay of Effective Date of a Final Rule Revoking Certification

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule; termination of stay.

**SUMMARY:** The Food and Drug Administration (FDA) is terminating the stay of the effective date of a final rule revoking the provisions for the certification of neomycin sulfate-sodium propionate otic solution. The basis for the revocation was that the drug product lacked substantial evidence of effectiveness. The effective date of the final rule was stayed pending review of a hearing request which has now been withdrawn.

**EFFECTIVE DATE:** May 26, 1982.

**FOR FURTHER INFORMATION CONTACT:** Douglas I. Ellsworth, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

**SUPPLEMENTARY INFORMATION:** In the Federal Register of September 19, 1974 (39 FR 33665), FDA published a final rule revoking § 444.442a (21 CFR 444.442a), which provided for the certification of neomycin sulfate-sodium propionate otic solution. The basis for the final rule was that the drug product lacked substantial evidence of effectiveness. The revocation was to take effect on October 29, 1974, unless a hearing was requested on the revocation. The final rule stated that if a hearing was requested, the effective date would be extended to allow for review of the hearing request.

In response, a hearing was requested for the following drug product:

NDA 50-364; Otobiotic Otic Solution containing neomycin sulfate and sodium propionate; Schering Corp., Galloping Hill Rd., Kenilworth, NJ 07033.

Accordingly, in a notice published in the Federal Register of March 14, 1975 (40 FR 11870), as amended by a notice published November 4, 1980 (45 FR 73034), FDA stayed the order revoking the portion of § 444.442a that provides for neomycin sulfate-sodium propionate otic solution.

Subsequently, Schering Corp. reformulated Otobiotic Otic Solution to an effective drug product containing polymyxin B sulfate and hydrocortisone (certified under 21 CFR 448.430), received FDA's approval of the new formulation, and withdrew its hearing request concerning the revocation of § 444.442a.

Therefore, under the Federal, Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-1051 as amended, 59 Stat. 463 as amended (21 U.S.C. 352, 357)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)) and redelegated to the Director, Bureau of Drugs (21 CFR 5.78), notice is given that the September 19, 1974 revocation, the effective date of which was extended by the March 14, 1975 notice, as amended by the November 4, 1980 notice, is effective May 25, 1982. All outstanding certificates for neomycin sulfate-sodium propionate otic solution are revoked and the regulation under which they were issued (21 CFR 444.442a) is revoked. No new certificates will be issued.

(Secs. 502, 507, 52 Stat. 1050-1051 as amended, 59 Stat. 463 as amended (21 U.S.C. 352, 357))

Dated: April 16, 1982.

**J. Richard Crout,**

*Director, Bureau of Drugs.*

[FR Doc. 82-13902 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

# Proposed Rules

Federal Register
Vol. 47, No. 101
Tuesday, May 25, 1982

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

## DEPARTMENT OF AGRICULTURE

### Agricultural Marketing Service

### 7 CFR Part 1106

### Milk in the Oklahoma Metropolitan Marketing Area; Proposed Suspension of Certain Provisions of the Order

**AGENCY:** Agricultural Marketing Service, USDA.

**ACTION:** Proposed suspension of rules.

**SUMMARY:** This notice invites written comments on a proposal to continue for an additional month a suspension of certain provisions of the Oklahoma Metropolitan Federal milk order. The proposed suspension, which would apply to June 1982, would reduce the amount of milk that a supply plant must ship to pool distributing plants in order to qualify as a pool plant. Also, the proposed action would increase the amount of milk that may be moved directly from farms to nonpool plants for manufacturing and still be priced under the order. The continuation of the earlier suspension for April and May was requested by a producer cooperative association because it is anticipated that milk production will continue to be considerably in excess of fluid milk sales in June.

**DATE:** Comments are due not later than June 1, 1982.

**ADDRESS:** Comments (two copies) should be filed with the Hearing Clerk, Room 1077, South Building, U.S. Department of Agriculture, Washington, D.C. 20250.

**FOR FURTHER INFORMATION CONTACT:** Robert F. Groene, Marketing Specialist, Dairy Division, Agricultural Marketing Service, U.S. Department of Agriculture, Washington, D.C. 20250, (202) 447-4824.

**SUPPLEMENTARY INFORMATION:** This proposed action has been reviewed under USDA procedures established to implement Executive Order 12291 and has been classified "not significant" and, therefore, not a major action.

It has been determined that any need for suspending certain provisions of the order on an emergency basis precludes following certain review procedures set forth in Executive Order 12291. Such procedures would require that this document be submitted for review to the Office of Management and Budget at least 10 days prior to its publication in the **Federal Register**. However, this would not permit the completion of the required suspension procedures in time for the suspension to be continued for June 1982 deliveries if this is found necessary. The initial request for this action was received on May 17, 1982.

It also has been determined that this proposed action would not have a significant economic impact on a substantial number of small entities. Such action would lessen the regulatory impact of the order on certain milk handlers and would tend to ensure that dairy farmers would continue to have their milk priced under the order and thereby receive the benefits that accrue from such pricing.

Notice is hereby given that, pursuant to the provisions of the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601 *et seq.*), the suspension of the following provisions of the order regulating the handling of milk in the Oklahoma Metropolitan marketing area is being considered for the month of June 1982.

**§ 1106.7 [Temporarily suspended in part]**

1. In § 1106.7(b), that part of the provisions that reads "until any month of such period in which less than 20 percent of the plant receipts and diverted milk specified previously herein is transferred to plants described in paragraph (a) of this section. A plant not meeting such 20 percent requirement in any month of such January–August period shall be qualified under this paragraph in any remaining month of the year only if transfers of fluid milk products (except filled milk) from the plant during the month to plant(s) described in paragraph (a) of this section are at least 50 percent of the plant receipts and diverted milk specified previously herein".

**§ 1106.13 [Temporarily suspended in part]**

2. In § 1106.13(e)(1), that part of the provisions that reads ", subject to the conditions of paragraph (e)(3) of this section, a total quantity of milk not in excess of total" and "received at all pool plants during the month. Diversions in excess of such quantity shall not be eligible under this section and the diverting cooperative shall specify the dairy farmers whose diverted milk is not so eligible. If the cooperative association fails to designate such persons, status under this section shall be forfeited with respect to all milk diverted by such cooperative association".

3. In § 1106.13(e)(2), that part of the provisions that reads ", subject to the conditions of paragraph (e)(3) of this section," and ", in a total quantity not in excess of the milk of producers not members of such cooperative association received at such pool plant(s) during the month. Milk diverted in excess of such quantity shall not be eligible under this section and the diverting handler shall specify the dairy farmers whose diverted milk is not so eligible. If a handler fails to designate such persons, status under this section shall be forfeited with respect to all milk diverted by such handler".

4. In § 1106.13, paragraph (e)(3).

All persons who desire to submit written data, views, or arguments in connection with the proposed suspension should file two copies of such material with the Hearing Clerk, Room 1077, South Building, United States Department of Agriculture, Washington, D.C. 20250, not later than June 2, 1982. The period for filing comments is limited to 7 days because a longer period would not permit the completion of the required suspension procedures in time for the suspension to be made effective for the month of June 1982.

The comments that are sent will be available for public inspection at the office of the Hearing Clerk during regular business hours (7 CFR 1.27(b)).

**Statement of Consideration**

The proposed suspension would continue for the month of June an identical suspension that was effective for April and May 1982. Under the proposed suspension, the amount of milk that supply plants must ship to pool distributing plants to attain pool plant status would be reduced in that only one shipment to a pool distributing plant would be needed to pool a supply plant. Also, the proposed action would increase the amount of milk that may be moved directly from farms to nonpool manufacturing plants and still be priced

under the order. Without the suspension, diversions would be limited to producers who deliver not less than 15 percent of their producer milk to pool plants. In addition, diversions to nonpool plants by proprietary handlers and cooperatives could not exceed the quantity of producer milk received at pool plants.

A continuation of the suspension was requested by a cooperative association that represents producers who supply the market. The cooperative indicated that the same imbalance between fluid requirements and production that existed in April and May is expected to continue in June. The cooperative stated that, although milk production appears to have reached its peak, there appears to be no indication of a decrease in production. Consequently, the cooperative anticipates that milk production will hold close to present levels well into June while fluid milk sales in June are expected to be below April and May levels due to schools being closed. Thus, the cooperative anticipates that greater than normal quantities of milk will have to be moved to manufacturing outlets for surplus disposal. In the absence of a continuation of the current suspension for the month of June, the cooperative contends that it would be necessary to make costly and inefficient movements of milk solely for the purpose of pooling the milk of dairy farmers who have regularly supplied the fluid milk needs of the market.

**List of Subjects in 7 CFR Part 1106**

Milk marketing orders, Milk, Dairy products.

Signed at Washington, D.C. on: May 20, 1982.

**William T. Manley,**

*Deputy Administrator, Marketing Program Operations.*

[FR Doc. 82-14231 Filed 5-24-82; 8:45 am]

BILLING CODE 3410-02-M

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Parts 172 and 189

**[Docket No. 81N-0292]**

## Cinnamyl Anthranilate; Proposed Prohibition of Use in Human Food

**AGENCY:** Food and Drug Administration.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to prohibit the use of cinnamyl anthranilate in human food. The proposal is based on a National Cancer Institute (NCI) study indicating that ingestion of cinnamyl anthranilate causes cancer in mice. The proposal would remove cinnamyl anthranilate from the list of food additives for direct addition to food for human consumption and would list cinnamyl anthranilate as a substance prohibited from use in food.

**DATE:** Comments by July 26, 1982.

**ADDRESS:** Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Donna A. Dennis, Bureau of Foods (HFF-335), Food and Drug Administration, 200 C St., SW., Washington, D.C. 20204, 202-472-4750.

**SUPPLEMENTARY INFORMATION:** Cinnamyl anthranilate ($C_{16}H_{15}NO_2$, CAS Reg. No. 87-29-6) is the ester of cinnamyl alcohol and anthranilic acid. It has been used since the 1940's in food and cosmetics as a component of imitation grape or cherry flavors and as a fragrance ingredient. In 1977, the U.S. International Trade Commission (Ref. 1) reported that the total U.S. sales of cinnamyl anthranilate in 1976 for use as a flavoring and as a fragrance ingredient was 2,000 pounds. In 1973, the National Academy of Sciences/National Research Council (NAS/NRC) (Ref. 2) reported that in 1970 approximately 700 pounds of cinnamyl anthranilate were used for flavoring food. The use of cinnamyl anthranilate in various food categories was reported by (1) the 1970 NAS/NRC survey (published in 1973) (Ref. 3) and (2) Hall and Oser (Ref. 4) as follows:

| Food category | Use level (parts per million) | |
|---|---|---|
| | NAS/NRC survey | Hall and Oser |
| Baked goods | 26 | 5.3 |
| Frozen dairy | 14 | 1.7 |
| Soft candy | 28 | 4.3 |
| Gelatins, puddings, and fillings | 32 | 28 |
| Alcoholic beverages and bases | 15 | (1) |
| Nonalcoholic beverages | 7 | 6.8 |
| Hard candy | 7 | (1) |
| Chewing gum | (1) | 46-730 |
| Miscellaneous, unclassified | 1 | (1) |

[1] None reported.

Cinnamyl anthranilate is listed as a direct food additive in § 172.515 *Synthetic flavoring substances and adjuvants* (21 CFR 172.515). This regulation was published in the **Federal Register** of October 27, 1964 (29 FR 14625) as 21 CFR 121.1164. In addition, in 1965, the Flavor Extract Manufacturers Association (FEMA) published a list of flavoring ingredients (Ref. 4), including cinnamyl anthranilate, that it considered to be generally recognized as safe for addition to food for human consumption. This list was based on two preliminary lists published by FEMA in 1960 and 1961.

The evidence used in 1964 to support the safe use of cinnamyl anthranilate in food included its previous history of use in food, the presence of other cinnamyl and anthranilate derivatives naturally in food and in natural substances used to flavor food, and some toxicological data, primarily acute toxicity data, to support the safety of some of these derivatives.

Recent studies on cinnamyl anthranilate include a study by Stoner et al. (Ref. 5) reporting that intraperitoneal administration of cinnamyl anthranilate produced primary lung tumors in a 24-week mouse pulmonary tumor response system. Following publication of this study, several short-term studies were performed in which cinnamyl anthranilate exhibited (1) low acute toxicity (its $LD_{50}$ in rats was greater than 5 g/kg body weight) (Ref. 6); (2) no mutagenicity in a bacterial assay (Ref. 7); and (3) no teratogenicity in a chicken embryo assay (Ref. 8). Cinnamyl anthranilate was selected for testing under the National Cancer Institute's Carcinogenesis Testing Program because of its use as a direct food additive and because of the results of the Stoner study. The National Institutes of Health issued a notice in the **Federal Register** of December 30, 1980 (45 FR 85832), announcing completion of the study and the public availability of the NCI bioassay report for cinnamyl anthranilate.

In the NCI report, "Bioassay of Cinnamyl Anthranilate for Possible Carcinogenicity" (Ref. 9), the results of this bioassay were summarized as follows:

A bioassay of cinnamyl anthranilate (a synthetic flavoring agent) for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were fed the test chemical in diets containing 15,000 or 30,000 ppm for 103 weeks and then observed for an additional 2 or 3 weeks. Controls consisted of groups of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed and necropsied at 105 to 107 weeks.

Mean body weights of the dosed male and female rats and mice were lower than those of the corresponding controls throughout the bioassay and weight decrements were dose related. Mortality in rats or mice of either sex was not affected by administration of the test chemical.

In male rats, adenocarcinomas or adenomas of the renal cortex and acinar-cell

carcinomas or adenomas of the pancreas were found in low incidences in dosed rats but not in control rats. In direct comparisons with matched control groups, the incidences of these tumors were not significantly increased; however, because these tumors rarely occur spontaneously in aging F344 rats, they were considered to be related to compound administration. Similar pancreatic or renal tumors have not been detected among 634 historical-control male F344 rats at the same laboratory.

In the female rats, no tumors occurred at incidences that could be clearly related to administration of the test chemical.

In both male and female mice, the incidences of hepatocellular carcinomas or adenomas were dose related (P less than 0.001) and significant (P less than or equal to 0.001) in direct comparisons of dosed and control groups.

It was concluded that under the conditions of this bioassay cinnamyl anthranilate was carcinogenic for male and female B6C3F1 mice, inducing increased incidences of hepatocellular carcinomas or adenomas. The test chemical was also carcinogenic for male F344 rats, inducing low incidences of acinar-cell carcinomas or adenomas of the pancreas and adenocarcinomas or adenomas of the renal cortex. Cinnamyl anthranilate was not carcinogenic for female F344 rats.

A copy of the National Cancer Institute's report, along with other information referenced in this document, has been placed on public display in the Dockets Management Branch (address above) and may be seen between 9 a.m. and 4 p.m., Monday through Friday.

The FDA Bureau of Foods' Cancer Assessment Committee (CAC) reviewed the reported NCI studies on the possible carcinogenicity of cinnamyl anthranilate in rats and mice. In its report (Ref. 10), the CAC notes that, in the mouse study, cinnamyl anthranilate induced a significant increase in the incidence of hepatocellular adenomas and carcinomas in both the male and female. The CAC concludes that these data, together with the presence of liver hyperplastic lesions in treated but not control animals, the shorter latency period for the onset of liver tumors in the treated groups, and the higher degree of malignancy of the tumors in treated groups, provide a convincing case for the carcinogenicity of cinnamyl anthranilate in mice.

The CAC notes, however, that in the rat study, there were no statistically significant increases in tumor incidence in treated groups compared to the controls. The CAC further notes that, in the high dose group, small increases occurred in the number of males bearing tumors at sites infrequently displaying spontaneous neoplastic lesions. The CAC considers that the presence of these tumors may be associated with compound treatment, but that the evidence is suggestive rather than conclusive.

As a result of this evaluation of the NCI study, the agency has concluded that cinnamyl anthranilate is carcinogenic to male and female B6C3F1 mice because it induces ademonas and carcinomas of the liver. The agency also has concluded that the small increases in the incidence of tumors of the kidney and pancreas in male F344 rats may also be related to treatment by cinnamyl anthranilate, but that conclusive evidence of this association is currently lacking.

Section 402(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 342(a)(2)(C)) defines a food as adulterated "if it is, or it bears or contains, any food additive which is unsafe within the meaning of section 409." Section 409(a) of the act (21 U.S.C. 348(a)) states that a food additive shall be deemed to be unsafe unless "there is in effect, and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used." In addition, section 409(c)(3)(A) of the act states that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *." On the basis of its analysis of the NCI report, FDA has concluded that cinnamyl anthranilate is a carcinogen when ingested by test animals. Therefore, the agency has concluded that cinnamyl anthranilate connot be approved as a food additive. Accordingly, under section 409 of the act, the agency is proposing to remove the listing of cinnamyl anthranilate in § 172.515 and is proposing a new regulation for cinnamyl anthranilate in Part 189 (21 CFR Part 189). Under this proposal, the addition of cinnamyl anthranilate to food would cause the food to be adulterated within the meaning of section 402(a) of the act and would subject the food to regulatory action. The agency expects to issue the appropriate final rule at the earliest possible date following the close of the comment period.

The agency concludes, however, that the protection of the public health does not require the recall of food (including intermediates) containing cinnamyl anthranilate from the market, or the destruction of food to which the substance has already been added. The agency has calculated an upper limit estimate of the risk presented by human ingestion of cinnamyl anthranilate at current levels of use. The agency utilized a linear proportional model, using the upper 99 percent confidence interval of the observed tumor incidence, as described in FDA's March 20, 1979 proposal, "Chemical Compounds in Food-Producing Animals" (44 FR 17070). According to this assessment, the upper limit of lifetime risk of cancer from ingestion of cinnamyl anthranilate at its previously reported levels of use is less than 1 in a million.

There are no fixed criteria for deciding whether to recall a product; each case must be judged on its own facts. The estimated risk cinnamyl anthranilate is low. Therefore, the agency believes that it is appropriate to permit the depletion of stocks of food products (including intermediates) containing cinnamyl anthranilate that were manufactured before the effective date of the final regulation.

The agency has carefully considered the potential environmental effects of this proposed action and has concluded that the action will not have a significant impact on the human environment. Therefore, an environmental impact statement is not required. The agency's findings of no significant impact and its environmental assessment may be seen in the Dockets Management Branch (address above), between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with the Regulatory Flexibility Act (Pub. L. 96-354), FDA has considered the effect that this regulation would have on small entities, including small businesses. The agency has determined that, although the proposed regulation would remove an approved additive from food, the effect of this action on small entities will be minimal. Only small amounts of cinnamyl anthranilate are currently used in food, and reformulation costs would be minimal because substitute ingredients are readily available. In addition, the agency has proposed no recall or destruction of products containing cinnamyl anthranilate that were manufactured before the effective date of the final regulation. The agency certifies that the publication of this proposal will not have a significant economic impact on a substantial number of small entities.

A decision on what, if any, regulatory

action should be taken on the use of cinnamyl anthranilate as an ingredient of drug and cosmetic products is being deferred until completion of the evaluation of skin penetration studies conducted by FDA and consideration of the total exposure to cinnamyl anthranilate from its use in these products.

**References**

The following information has been placed on public display in the Dockets Management Branch (address above), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. United States International Trade Commission (1977), *Synthetic Organic Chemicals—United States Production and Sales, 1976,* USITC Publication 833, U.S. Government Printing Office, Washington, DC.

2. National Academy of Sciences/National Research Council (1973), *A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized as Safe:* Table 11: Part C—Annual Poundage Data for FEMA Questionnaire Substances Not Listed in NAS Appendix A (Group III). National Technical Information Service, Springfield, VA, Order No. PB 221-936.

3. National Academy of Sciences/National Research Council (1973), *A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized as Safe:* Table: Maximum Usage Levels Reported in NAS-GRAS Phase II Survey—by Substance, Food Category, and Technical Effects, Group B: FEMA Questionnaire Substances not in Appendix A.

4. Hall, R. L. and B. L. Oser, "Recent Progress in the Consideration of Flavoring Ingredients under the Food Additives Amendment. III. GRAS Substances," *Food Technology,* 19:151-197, 1965.

5. Stoner, G. D., M. B. Shimkin, A. J. Kniazeff, J. H. Weisburger, E. K. Weisburger, G. B. Gori, "Test for Carcinogenicity of Food Additives and Chemotherapeutic Agents by the Pulmonary Tumor Response in Strain A Mice," *Cancer Research,* 13:751-752, 1973.

6. Opdyke, D. L. J., "Cinnamyl Anthranilate," *Food and Cosmetics Toxicology,* 13:751-752, 1975.

7. Litton Bionetics, Inc. (1975), *Mutagenic Evaluation of Compound FDA 73-59 Cinnamyl Anthranilate.*

8. Food and Drug Administration (1976), "Investigations of the Toxic and Teratogenic Effects of GRAS Substances to the Developing Chicken Embryo: Cinnamyl Anthranilate."

9. National Cancer Institute (1980), "Bioassay of Cinnamyl Anthranilate for Possible Carcinogenicity," Technical Report No. 196, DHEW Publication No. (NIH) 80-1752, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD.

10. Cancer Assessment Committee, Bureau of Foods, Food and Drug Administration (1980). Memorandum of meeting, "Cinnamyl anthranilate."

**List of Subjects in 21 CFR**

*Part 172*

Food additives; Food preservatives; Spices and flavorings.

*Part 189*

Food ingredients.

Therefore, under the Federal Food, Drug, and Cosmetic Act (Secs. 201(s), 402, 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 342, 348, 371(a))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), it is proposed that Parts 172 and 189 be amended as follows:

## PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

**§ 172.515 [Amended]**

1. Part 172 is amended in § 172.515 *Synthetic flavoring substances and adjuvants* by removing the entry for "cinnamyl anthranilate".

## PART 189—SUBSTANCES PROHIBITED FROM USE IN HUMAN FOOD

2. Part 189 is amended by adding new § 189. 113 to read as follows:

**§ 189.113 Cinnamyl anthranilate.**

(a) The food additive cinnamyl anthranilate ($C_{16}H_{15}NO_2$, CAS Reg. No. 87-29-6) is the ester of cinnamyl alcohol and anthranilate acid. Cinnamyl anthranilate is a synthetic chemical that has not been identified in natural products at levels detectable by available methodology. It has been used as a flavoring agent in food.

(b) Food containing any added cinnamyl anthranilate is deemed to be adulterated in violation of the act based upon an order published in the Federal Register of (insert date and reference for publication of the final rule).

Interested persons may, on or before July 26, 1982 submit to the Dockets Management Branch (address above), written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: April 13, 1982.

**Arthur Hull Hayes, Jr.,**

*Commissioner of Food and Drugs.*

[FR Doc. 82-14165 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## 21 CFR Part 452

**[Docket No. 79N-0459]**

## Erythromycin Estolate: Withdrawal of Proposal to Revoke Provisions for Certification of Tablets and Capsules; Response to Petition; Labeling

**AGENCY:** Food and Drug Administration.

**ACTION:** Withdrawal of proposed rule.

**SUMMARY:** The Commissioner of Food and Drugs announces that he has completed his review of the administrative record concerning the safety of erythromycin estolate. The Commissioner concludes that the drug is safe in that the risks of hepatotoxicity do not outweight its therapeutic benefits. Accordingly, the Commissioner withdraws a proposal to revoke provisions for certification of adult dosage forms of erythromycin estolate and in a related document published elsewhere in this issue sets forth the labeling changes. In addition, the Commissioner denies a petition requesting that all dosage forms of erythromycin estolate be removed from the market.

**DATES:** Withdrawal of the proposal to revoke provisions for certification is effective May 25, 1982.

**ADDRESS:** The transcript of the public hearing before the advisory committee, evidence and comments submitted, and all other documents listed in this notice may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, from 9 a.m. to 4 p.m., Monday through Friday.

**FOR FURTHER INFORMATION CONTACT:** Suzanne O'Shea, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

**SUPPLEMENTARY INFORMATION:** This notice withdraws the proposal of the Director of the Bureau of Drugs to revoke provisions for certification of adult dosage forms of erythromycin estolate (tablets—21 CFR 452.115a, capsules—21 CFR 452.115b). The basis of the proposal was that erythromycin estolate is unsafe because of the risks of hepatotoxicity (adverse liver effects) associated with its use, particularly in light of the availability of other erythromycins indicated for the same conditions which do not cause hepatotoxicity. The proposal described new evidence suggesting that the estolate may be less bioavailable than other erythromycins. In addition, the proposal asserted that there are no other significant therapeutic benefits peculiar

to the estolate which would justify its continued certification. Thus, the proposal asserted that the risks of the drug had been tentatively found to outweigh its benefits. The effect of the Director's proposal, if finalized, would have been removal of adult forms of erythromycin estolate from the market.

This notice also denies a petition submitted by Health Research Group (HRG), a consumer-oriented organization interested in the regulation of drugs. Using a rationale similar to the Director's, the petitioner requested that all dosage forms of erythromycin estolate be removed from the market. This request included the pediatric dosage forms: oral suspension, pediatric drops, and chewable tablets.

The Commissioner has reviewed data submitted by the manufacturers of erythromycin estolate, HRG, and the Bureau of Drugs (Bureau). He has reviewed the presentations made at a public hearing before the Ad Hoc Advisory Committee on Erythromycin Estolate (Committee). In addition, the Commissioner has considered the 763 comments that were submitted on the proposal.

The Committee found that, for adult and pediatric dosage forms of erythromycin estolate, the risks do not outweigh the benefits. The Commissioner accepts the Committee's recommendations which state that both adult and pediatric dosage forms of the estolate have a favorable risk/benefit ratio. Specifically, he concludes that the estolate is associated with a higher incidence of hepatotoxicity than other erythromycins, but this risk is offset by more reliable initial absorption, which may be important in serious infections, and by lack of significant effect of food on absorption.

## I. Introduction

### *A. The Drug*

Erythromycins belong to the macrolide group of antibiotics. They are alternative therapy for certain treatment and prophylaxis of diseases in patients allergic to penicillin. Erythromycins are also used in the treatment of Legionnaire's disease, pertussis, diptheria, intestinal amebiasis, primary syphilis, upper and lower respiratory tract infections, skin and soft tissue infections caused by susceptible organisms.

There are four types of erythromycin in solid dosage form currently available: erythromycin base, erythromycin ethyl succinate, erythromycin stearate, and erythromycin estolate. Erythromycin base, the original erythromycin formulation, was discovered in 1952. Gastric acidity has an inactivating effect on erythromycin base. Many erythromycin base products are, therefore, coated to help prevent inactivation. The stearate salt and the ethyl succinate ester of erythromycin were developed a few years later, in an attempt to overcome the problem of absorption associated with the base.

Erythromycin estolate was formulated in the late 1950's in an attempt to provide a form of erythromycin that would be more reliably absorbed than the base, stearate, or ethyl succinate. It is the lauryl sulfate salt of the propionyl ester of erythromycin base. Because of acid stability, it is not inactivated by gastric juices. After oral administration, erythromycin estolate is in the blood as free erythromycin base and as propionyl erythromycin ester. The propionyl ester hydrolyzes to the free base form of erythromycin.

Dista Products Co., Division of Eli Lilly & Co., P.O. Box 1407, Indianapolis, IN 46206 (Lilly) is the major producer of erythromycin estolate. The antibiotic forms (applications) for Lilly's adult dosage forms currently marketed tablets and capsules are numbered 61–896; 500 mg tablets, and 61–897; 125 mg and 250 mg capsules. The trade name for its erythromycin estolate products is Ilosone. Most of the studies presented and reviewed were conducted with Ilosone. This notice refers to erythromycin estolate rather than Ilosone, however, because the data pertain to all brands of estolate.

Erythromycin estolate capsules (250 mg) are also currently marketed by Danbury Pharmacal Inc., 131 West St., P.O. Box 296, Danbury, CT 06810, under antibiotic form 62–087.

Since the hearing before the Committee, FDA has approved the applications of two additional manufacturers:

1. 62–162; 125 mg and 250 mg capsules, Barr Laboratories, Inc., 265 Livingston St., Northvale, NJ 07647.
2. 62–237; 250 mg capsules, Zenith Laboratories, 140 LeGrand Ave., Northvale, NJ 07647.

### *B. Regulatory History*

Erythromycin estolate was first approved for marketing in 1958. It was one of the drugs reviewed in the Drug Efficacy Study. In the **Federal Register** of August 29, 1970 (35 FR 13803), October 14, 1971 (36 FR 19988), and September 17, 1976 (41 FR 40209), the agency classified the drug as effective in the treatment of various infections.

The hepatic potential of the estolate has been of concern to the agency for many years. The first report of hepatotoxicity associated with the estolate was published in 1961. In 1962, the package insert was revised to add information about the recognized hepatotoxicity with the estolate. The firm sent two "Dear Doctor" letters to health professionals concerning the hepatotoxicity of the estolate—one in 1961, the second in 1963.

1. *The 1973 action.* In April 1973, HRG submitted a petition requesting that all dosage forms of erythromycin estolate be withdrawn from the market. The petition stated that the estolate causes serious hepatic effects not caused by other erythromycins without conferring any offsetting advantage.

In May 1973, FDA's Anti-Infective Advisory Committee met to discuss the safety and effectiveness of erythromycin estolate. The Committee found that hepatotoxicity was associated only with the estolate, not the other forms of erythromycin. It found, however, that when given in lower doses, the estolate was an effective as other erythromycins for streptococcal infections and primary syphilis (Refs. 12, 13, and 71). The Committee rejected the sore throat study submitted by HRG in which the estolate, stearate, and ethyl succinate were equally effective because no microbiological confirmation of etiology was made (Ref. 128).

Thus, the Committee concluded that the estolate's higher blood levels had been correlated with greater effectiveness, and that the estolate's risk/benefit ratio was favorable. The Committee also concluded that children appear to be immune to estolate toxicity. It recommended to FDA that the safety of adult dosage forms of erythromycin estolate did not warrant removing them from the market, but also recommended that the hepatotoxicity warning be strenghtened in the estolate labeling. The Commissioner accpeted the Committee's findings and, as a consequence, the package insert for erythromycin estolate was revised again, this time to include a boxed warning of its hepatotoxic potential.

2. *The 1979 Action.* In 1978, the Bureau obtained new data indicating that the blood levels of free erythromycin base may be actually lower than for the estolate than for other erythromycins. In addition, upon review of FDA's file of nationwide spontaneously reported adverse drug reactions (ADR reports), it appeared that of the reports of hepatotoxicity due to some oral erythromycin product, 93 percent had hepatotoxicity associated with the estolate, a proportion much greater than the estolate's market share. Further, the Bureau knew of no studies indicating that the estolate is clinically more

effective than other erythromycins. Thus, it appears that the greater hepatoxicity of erythromycin estolate was not counterbalanced by greater bioavailability of clinical effectiveness, and on a benefit/risk basis the estolate was less safe than other forms of erythromycin.

By letter of August 29, 1979, the agency requested that Lilly voluntarily remove all dosage forms of the drug from the market. The agency made the same request of Danbury by letter dated September 10, 1979. In response to the letters, Lilly asserted that erythromycin estolatge is safe and effective, and declined to voluntarily withdraw the products from the market. Danbury responded that the estolate is safe and effective, but stated that if the estolate were demonstrated to be unsafe, it would voluntarily withdrew it from the market.

On August 30, 1979, HRG submitted a second petition requesting the withdrawal from the market of all dosage forms of erythromycin estolate. Again, the basis of the petition was that the estolate causes hepatic reactions not caused by other erythromycins, and that there is no offsetting advantage to the estolate.

In the **Federal Register** of December 4, 1979 (44 FR 69670), the Director of the Bureau of Drugs proposed to revoke the provisions for certification of adult dosage forms of erythromycin estolate, stating that the drug appears to cause significantly more hepatic reactions, is less bioavailable, and is clinically no more effective than other erythromycins. The notice stated that comments would be accepted until January 3, 1980.

The pediatric dosage forms (chewable tablets, pediatric drops, and oral suspensions) were not included in the proposal. From the data available it appeared that the prevalence of hepatic reactions in young children is much less than in adults. Further, it was not clear that the number of hepatic reactions in relation to usage in young children was different for the different salts and esters of erythromycin.

The December 4, 1979 proposal stated that interested persons could submit a request for an informal conference on the proposed revocation. The agency received one request for an informal conference and two requests for an extension of the comment period. In the **Federal Register** of January 4, 1980 (45 FR 1085), the Director announced that because of the controversial nature of the proposal, he would grant the request for an informal conference. The comment period was extended to February 4, 1980.

The informal conference was held on January 18, 1980. At the conference, presentations were made by Lilly, Barr Laboratories, and two individuals. A transcript of the conference may be seen at the Dockets Management Branch under docket number 79N-0459.

*C. The Ad Hoc Committee on Erythromycin Estolate*

In order to assure that the factors determining the risks and benefits of erythromycin estolate were as fully developed as possible before a final determination was made, the agency decided to submit the substantive issues to an independent scientific review by an advisory committee. Because the charter of the appropriate standing advisory committee has expired, the Commissioner chartered, in the **Federal Register** of June 10, 1980 (45 FR 39340), the Ad Hoc Advisory Committee on Erythromycin Estolate (Committee) to review information pertaining to adult and pediatric dosage forms of erythromycin estolate and to advise the agency on the determination of the benefit/risk ratio of all dosage forms.

In a notice published in the **Federal Register** of February 27, 1981 (46 FR 14355), the Commissioner announced that a public hearing before the Ad Hoc Committee would be held on April 16-17, 1981. The Commissioner asked manufacturers, the Bureau of Drugs, and other interested persons to make written submissions of data for consideration by the Committee, and to be prepared to make oral presentations at the hearing. The Commissioner also set out the specific issues to be considered by the Committee:

1. Whether the prevalence of adverse liver effects from erythromycin estolate is greater for adults or children, or both, than that for other erythromycins; if so, whether the difference is clinically significant.

a. Whether voluntary adverse drug reaction reports can reliably be used to determine the relative prevalence of adverse liver effects for erythromycins; if so, what differences they show in the relative prevalence of those effects and whether the differences are clinically significant.

b. Whether data that are presented from the Kaiser-Permanente Study, or from any other retrospective study, can reliably by used to determine the relative prevalence of adverse liver effects for erythromycins; if so, what differences the data show in the relative prevalence of those effects and whether the differences are clinically significant.

c. Whether data that are presented from any prospective clinical study can reliably be used to determine the incidence of adverse liver effects for erythromycins; if so, what differences the data show in the relative incidence of those effects and whether the differences are clinically significant.

2. Whether there are any differences among erythromycins in the prevalence of adverse effects in adults or in children, or both, other than those involving the liver (for example, gastrointestinal intolerance); if so, whether those differences are clinically significant. Please state the basis for your conclusions.

3. For every bioavailability/bioequivalence study that is presented, the Committee is asked to comment on the adequacy of the design for determining bioavailability/bioequivalence, and whether the Committee believes the results of the study can be relied on to draw conclusions about comparative bioavailability of erythromycins under actual conditions of medical practice. The Committee will also address the following questions:

a. Whether tissue concentration studies of erythromycin estolate and erythromycin ethylsuccinate provide any evidence of clinically significant advantage for adults or children. Please identify the specific studies on which your conclusions are based.

b. Whether studies showing observable higher blood levels of erythromycin as the estolate indicate that erythromycin estolate is more reliably absorbed than other erythromycins and whether the studies provide any evidence of clinically significant advantage for adults or children. Please identify the specific studies on which your conclusions are based.

c. Whether erythromycin estolate, measured as the base, provides higher, the same, or lower blood levels that other erythromycins measured as the base; whether, as so measured, erythromycin estolate is more, equally, or less reliably absorbed than other erythromycins; and whether the differences, if any, are clinically significant. Please identify the specific studies on which your conclusions are based.

4. Whether the propionyl ester of erythromycin estolate, apart from its being hydrolyzed, contributes to the therapeutic effect of erythromycin estolate; if so, why. Does it, for example, have an antibacterial effect? Whether, if the propionyl ester contributes to the therapeutic effect of erythromycin estolate, it has been demonstrated to convey a clinical advantage over other

erythromycins. Please state the basis for your conclusion.

5. Whether a prospective study to determine the therapeutic effect (for example, antimicrobial) of the propionyl ester portion of the estolate molecule is feasible and needed; if so, what the design of such a study should be.

6. Whether erythromycin estolate has been shown in clinical practice to offer any therapeutic advantage in adults or children over other erythromycins.

a. Whether erythromycin estolate has been shown to be effective at lower doses than other erythromycins in the treatment of streptococcal infections and primary syphilis; if so, whether this use of lower doses offers any clinical advantage. Please state the basis for your conclusion.

b. Whether erythromycin estolate has been shown to be more effective than erythromycin ethylsuccinate in the treatment of *Haemophilus influenzae* otitis media. Please state the basis for your conclusion.

c. Whether erythromycin estolate has been shown to have any advantage over other erythromycins in the treatment of diphtheria, pertussis, Legionnaires disease, chlamydial infections, and *Campylobacter* enteritis. Please state the basis for your conclusion.

7. On the basis of the evidence presented, whether erythromycin estolate has a better, the same, or a poorer benefit/risk ratio in adults than other available erythromycins. Please state the basis for your conclusion.

8. If erythromycin estolate has a favorable risk/benefit ratio in adults, what labeling changes, if any, are recommended for adult dosage forms of erythromycin estolate.

9. On the basis of the evidence presented, whether erythromycin estolate has a better, the same, or a poorer benefit/risk ratio in children than erythromycin ethylsuccinate. Please state the basis for your conclusion.

10. If erythromycin estolate has a favorable risk/benefit ratio in children when compared to erythromycin ethylsuccinate, what labeling changes, if any, are recommended for pediatric dosage forms of erythromycin estolate.

The Committee's report was submited on July 24, 1981. In order to allow public comment on the Committee's report, the comment period was extended by notice published in the **Federal Register** of July 28, 1981 (46 FR 38536) to August 18, 1981.

## II. Comments Submitted on The Proposal

The agency received 763 comments on the proposal. Comments were received from 17 State boards of pharmacy or pharmaceutical associations, 14 State medical associations, 4 State osteopathic associations, 1 local osteopathic association, 3 State dental associations, 2 State academies of family physicians, 13 county medical associations, and 7 national associations including the American Medical Association and the American Pharmaceutical Association. Lilly submitted comments on January 31, 1981. The remaining comments were from individual practitioners.

1. The American Pharmaceutical Association took no position on the substantive issues related to the proposal. Rather, the association asserted that a final rule revoking provisions for certification taking effect on the date of publication, as proposed, would lead to substantial confusion on the part of health care practitioners, with resulting disruption of patient care. The association requested that the final rule not take effect until after a reasonable period of time to establish alternative drug therapy for patients under treatment.

The provisions for certification of the estolate tablets and capsules are not being revoked. Thus, it is not necessary to consider the impact of the effective date of a final rule revoking certification provisions.

2. Many of the comments, from associations as well as individuals, requested that the agency submit the issue of the safety of the estolate to an advisory committee before making a final decision.

The issues involved in the determination of the risks and benefits of the estolate were submitted to an advisory committee for independent scientific review. The Committee's conclusions are set forth below.

3. The majority of the comments from practitioners objected to the Bureau's propoasl and requested that the estolate remain on the market. The objections were based on years of personal experience with the estolate with little evidence of hepatic reaction. The agency received three comments supporting its proposal. These comments were also based on the personal experience of the commenters.

4. In its comments Lilly claimed that the proposal was based on an erroneous legal premise—that of relative efficacy. The firm charged that although the proposal was ostensibly based on a conclusion that the estolate is not safe, in actuality it is based only on comparisons of the estolate's bioavailability (essentially an effectiveness determination) with that of other erythromycins. According to Lilly, actions against drugs based on assertions that other drugs are more effective are prohibited by the Federal Food, Drug, and Cosmetic Act.

Lilly misconstrues the agency's action and the nature of a safety determination when it charges that it is engaging in a determination of relative efficacy. The determination of the safety of a drug often includes a determination of its risks and benefits. To the extent that benefits involve effectiveness, safety determinations unavoidably involve some consideration of effectiveness. Certain side effects may be judged to be acceptable when balanced against the potential benefits of a drug. Further, if the drug under consideration is one of a class of drugs indicated for the same conditions, the safety of the one drug cannot be determined without consideration of the safety of the others. A somewhat greater incidence of side effects may be tolerated in the drug under consideration, as compared the class as a whole, if those side effects are sufficiently offset by greater benefits, when compared to the class as a whole. This balancing test is improperly characterized as relative efficacy.

In this case, then, the safety of the estolate was at issue. A somewhat greater incidence of side effects (safety considerations) had been tolerated in the estolate because they were thought to be offset by greater benefits when compared to other drugs in the class. When the agency tentatively determined that the benefits were no greater than the class, it was the estolate's greater potential for harm that resulted in the proposed revocation.

## III. Summary of Data Presented

At the hearing, data were presented by the Bureau of Drugs, Lilly, HRG, and 10 individuals. The most significant data presented by HRG (in its petition and at the hearing), the Bureau, Lilly, and interested persons are summarized below. Data presented by individuals are specifically described only when they differ significantly from the data presented by the Bureau, Lilly, or HRG.

### HRG Petition and Presentation of Data

#### *A. Incidence of Hepatic Reactions*

HRG asserted that the risks of hepatotoxicity from erythromycin estolate outweigh its therapeutic benefits. It requested that all dosage forms be removed from the market. It cited the Bureau's figures from voluntary adverse drug reaction (ADR) reports indicating that hepatic reactions (hepatitis, jaundice, cholestatic jaundice, abnormal liver function) occur 45 times more frequently with the estolate than with generic erythromycin, 16 times

more frequently than with Erythrocin (film-coated erythromycin base, manufactured by Abbott Laboratories), and 6.9 times more frequently than with erythromycin ethyl succinate. Thus, patients who use the estolate are roughly 20 times more likely to suffer drug-associated hepatotoxicity than if they were to use another form of erythromycin. At the hearing HRG asserted that even if only one in a thousand people taking the estolate has a hepatic reaction, it would amount to over 3,500 cases a year in the United States (3.8 million prescriptions were filled in 1980).

The petitioner also described a study undertaken in 1977 said to demonstrate the toxicity of erythromycin estolate (Ref. 1). Of a group of pregnant women receiving 250 milligrams (mg) of the estolate for three weeks or longer, 14.4 percent developed subclinical, reversible hepatic toxicity. Of the 97 patients who received erythromycin stearate, only 3 percent developed abnormal SGOT levels (a test measuring hepatic dysfunction). The investigators stated that there was no convincing evidence that erythromycin estolate offered any clinical advantage.

*B. Description and Effects of Hepatotoxicity*

The petitioner cited the 1977 AMA Council of Drugs *Drug Evaluation Book* (3rd ed.) and Goodman and Gilman, *The Pharmacologic Basis of Therapeutics*, which state that hepatotoxicity is associated only with the estolate. The petitioner also quoted two patients who had suffered an hepatic reaction to the estolate. "These reactions are not mild; I was incapacitated for five weeks because of the liver reaction." Another said, "I became more ill than I've ever been in my entire life."

At the hearing Dr. Fenton Schaffner, Chief of the Division of Liver Disease in the Department of Medicine at Mount Sinai School of Medicine, appeared on behalf of HRG. Dr. Schaffner stated that even though there is no evidence of resulting chronic liver disease and only a few persons are affected each year, there is a significant amount of time lost and cost to the community. For these reasons, he supported removing the drug from the market.

Petitioner contended that hepatic reactions to the estolate, though reversible, are not benign. It cited five cases in the literature where unnecessary surgery resulted from a reaction to the estolate and contended that more cases of unnecessary surgery have, no doubt, occurred than are ever reported (Refs. 2 through 6).

*C. Bioavailability and Clinical Effectiveness*

HRG contended that the higher blood levels obtained with the estolate (free base and estolate levels combined) do not translate into therapeutic superiority. The petitioner cited several studies demonstrating that the estolate is hydrolyzed to free base only to the extent of 20 to 25 percent (Refs. 7, 8, and 9). In addition, HRG contended that the estolate is protein-bound to a higher degree than other erythromycins and, therefore, less likely to be of therapeutic benefit. By comparison, in one study the percent of nonprotein-bound and, therefore, available, drug was seven times greater with the base than with the estolate (Ref. 10). Another investigator found that the percent of free drug was approximately four times greater with administration of the base than with the estolate (Ref. 11).

HRG also contended that no substantial differences have been found in studies comparing the clinical effectiveness of the different erythromycins in the treatment of variety of infections. In 1973 the Commissioner concluded that the estolate was more effective than the base because 30 grams (g) of base were no more effective than 20 g of the estolate in treating primary syphilis. HRG noted, however, that these were not studies of clinical effectiveness, but rather of the 12 month re-treatment rate. The investigators found that the patients given the base had a re-treatment rate of 9.9 percent (Ref. 71), while the patients given estolate had a 14.8 percent re-treatment rate (Ref. 12).

Another study demonstrated that 20 mg/lb of the ethyl succinate was as effective as 7.5 mg/lb of the estolate in treating streptococcal sore throats (Ref. 13). A study comparing the effectiveness of the estolate, the ethyl succinate, and the stearate in 305 patients reported, "The microbiologic failure rates and recurrence rates in patients with Group A beta-hemolytic streptococcal infections of the upper respiratory tract did not differ significantly among three forms of erythromycin . . . ." (Ref. 14) A 1975 study of gonorrhea showed recurrences in 24 percent of the patients treated with the estolate and 23 percent of the patients treated with the base (Ref. 8). The final study presented by HRG was conducted in Australia and purported to show a lower rate of recurrence of strep throat due to estolate suspension (Ref. 15). However, the study was found by the Australian Drug Evaluation Committee not to show any "statistically significant or clinically important" differences between the estolate and stearate suspensions.

HRG asserted that there is no convincing evidence substantiating the claim that the estolate is better tolerated because fewer gastrointestinal side effects occur with it than with other erythromycins. One study compared equal doses of the estolate and the base (Ref. 8). Gastrointestinal side effects were common with both forms, though they were somewhat more common with the base.

Another study obtained opposite results in the comparison of the estolate, the ethyl succinate, and the stearate (Ref. 14). Most adverse reactions occurred in the patients who took the estolate. A third study found no major gastrointestinal adverse effects with either the estolate or the ethyl succinate in 182 patients (Ref. 16).

*D. Pediatric Dosage Forms*

HRG requested that all dosage forms of erythromycin estolate be removed from the market. It included the pediatric dosage forms, asserting that the amount of drug-induced liver damage in children is not insignificant. Petitioner suggested, in addition, that liver disease in children may be reported less frequently than in adults because the disease may be less frequently accompanied by jaundice in children than in adults. Thus, many children who actually suffer liver damage from the estolate may not come to medical attention.

HRG suggested that a further problem with pediatric use of the estolate is the possibility of widespread sensitization. As the children who have been treated with the drug grow to adulthood, subsequent doses could initiate a much higher percentage of toxic reactions than have occurred in today's adults, few of whom were given the drug as children.

HRG noted that the estolate has already been removed from the market in several other countries: in Australia in 1973, in Sweden in 1974, in Denmark in 1975, and in the Netherlands in 1976. No sales have been reported in Austria since February 1980.

In light of these data, HRG concluded that erythromycin estolate is a dangerous and completely unnecessary drug that has been marketed much to long already. They urged the agency to remove all dosage forms as quickly as possible.

**Bureau of Drugs' and Lilly's Presentation of Data**

Data supporting the Bureau's proposal to discontinue certification of erythromycin estolate are summarized

below. Data submitted by Lilly challenging the proposal are also summarized below. The summary includes data submitted by Lilly on October 25, 1979, to the FDA Advisory Committee on Anti-Infective Drugs, on January 18, 1980 at the informal conference, on January 31, 1980, in response to the December 14, 1979 proposed rule, and on March 30, 1981, for submission to the Committee and discussion at public hearing in April 1981.

*A. Adverse Reactions*

Information on the estimates of rates of occurrence of hepatic reactions caused by the various erythromycins was derived from three primary sources: the agency's spontaneous, nationwide adverse drug reaction (ADR) reporting system, a retrospective study of patient records at the Kaiser-Permanente Medical Care Program in Oakland, California, and a review of Medicaid claims records of the States of Michigan and Texas.

Manufacturers are required under 21 CFR 310.301 to submit reports of adverse reactions to the agency's ADR reporting system. Reports from manufacturers are augmented by direct reports from the medical community, the medical literature, contract studies, and foreign data. The reports are evaluated with respect to causality and placed into three general categories: new serious, known serious, and not serious. All reports are placed in a computer file where they can be used to tabulate events thought to be drug-associated and to develop demographic profiles of an effect on the population (Ref. 17).

The study of patient records at the Kaiser-Permanente Medical Care Program (a health maintenance organization) in Oakland, California (K-P study) was commissioned by Lilly in response to the December 4, 1979 proposal (Ref. 18). That study was completed on February 6, 1981. In the study, trained medical record analysts reviewed the records of outpatients during and following 1,078 courses of estolate therapy and 2,583 courses of non-estolate therapy for any evidence of hepatic reactions. The investigators found one probable case of cholestatic hepatitis due to the estolate, and four possible cases due to non-estolate erythromycin.

The Medicaid studies are reviews of patient records under Medicaid. State records are kept of drugs dispensed and physician diagnoses by date of service (Ref. 19). Lilly carried out a study of the Texas and Michigan Medicaid systems. In Texas, the rates of hepatic-related events were 1.9 per thousand adults exposed to the estolate, and 1.86 per thousand adults exposed to non-estolate erythromycin. In Michigan, rates were 4.3 per thousand for the estolate and 2.97 per thousand for non-estolate.

1. *The ADR Reports.*

a. *Bureau of Drugs' Position.* The Bureau made no assertions about the absolute prevalence of the hepatic reactions caused by the estolate and other erythromycins. It did contend, however, that relative prevalence may be estimated from ADR reports because the reporting reflects the actual occurrence of reactions, and on this basis found that relatively more hepatic reactions are caused by the estolate than by other erythromycins.

To estimate the differences in rates of adverse reactions between the estolate and other erythromycins, the Bureau combined ADR data with data on the market share of the drugs. These data were obtained from IMS America's National Prescription Audit and the National Disease and Therapeutic Index. The agency studied the years 1974 (the first year for which market share data were collected) to 1979 (the last year for which market share data were available).

In the 1974–1979 period the Bureau received 315 ADR reports for all salts and esters of erythromycin. If hepatoxicity were equal for estolate and non-estolate erythromycins, then the distribution of ADR reports should follow the market share. An observed/expected ratio can thereby be developed.

The Bureau found that in adults and older children (over 9 years) the average observed/expected ratio for the estolate was 5.2; that is, hepatic reactions were reported 5.2 times more frequently than would be expected based on the market share. Conversely, the average observed/expected ratio in adults for non-estolate erythromycins was 0.19. The difference in these ratios is approximately 27-fold.

In children, (under 9 years) the observed/expected ratio for the estolate was 2.8, while for other erythromycins the ratio was 0.13, a 22-fold difference. The Bureau noted that, because of the very small number of adverse reactions reported for children, these estimates are necessarily imprecise.

The Bureau acknowledged possible weaknesses in this type of data. A chronic problem is the low reporting rate. However, because of the large U.S. population, even rare events are reported a significant number of times over a period of years. Another problem is the variable quality of the data. In the past few years, however, the Bureau has been able to define the kind of information required to make inferences from these data.

The Bureau also acknowledged that the most difficult problem with ADR reports is bias. ADR reports may be used to estimate relative frequency of adverse reactions when there is no major association of an effect with one type of drug in a particular group, there is no major intrinsic bias for reporting on one demographic group as opposed to another, and there in no external biasing factor that would stimulate detection and reporting (e.g., a literature report suggesting the possibility of a previously unsuspected association—the "bandwagon" effect).

A characteristic of this latter bias is that it is not thought to be consistent over time. Therefore, the Bureau argued that if the proportion of reports attributed to the estolate were consistent over a period of years, it can be inferred that the reports reflect actual occurrences and are not due to some sort of bias. The absolute number of reports of hepatic reactions to any erythromycin between 1974 and 1979 was variable, from a low of seven reports in 1979 to a high of 72 reports in 1976. It is noteworthy, however, that the estolate observed/expected ratio (for children and adults, combined) is consistently in the range of three to four times that expected. This is in contrast to the non-estolate erythromycins, which have an observed/expected ratio consistently under unity, ranging from 0.07 in 1974 to 0.67 in 1979.

As a check on the system, the Bureau analyzed the data over time, across demographic characteristics other than the child/adult distinction. For example, in the estolate, the average sex-related observed/expected ratio for males was 0.7; the range is from a high of 1.1 in 1978 to a low of 0.5 in 1975. The average estolate observed/expected ratio for females is 1.3, ranging from a high of 2.0 in 1979 to a low of 1.0 in 1978. These figures are consistent with the hypothesis that women are somewhat more susceptible to hepatic reactions than men, but the important characteristic is the consistency of the figures over time. If the distribution between men and women were very inconsistent from year to year, it could be inferred that some factor other than actual occurrences was stimulating reports.

Similarly, the Bureau examined reports of rashes over time associated with the erythromycins as an additional check on the system. The Bureau found, in children and adults, that the distribution of reports for estolate versus non-estolate tended to

approximate market share year by year. This consistent finding suggests that there was no systematic relative over-reporting of non-hepatic adverse effects associated with erythromycin estolate.

The Bureau discussed briefly ADR data available from foreign countries. The ADR reports from Sweden and Japan corroborated the Bureau's findings: the observed/expected ratios relative to market share for the estolate were 3.7 and 1.7, respectively; and for the non-estolate erythromycins the ratios obtained in both countries were less than one.

b. *Lilly's Position.* Lilly challenged the Bureau's reliance on ADR data, stating that the quality of this information is inferior to data from the K–P and Medicaid studies. The firm stated that ADR data cannot be used to determine the relative frequency of adverse effects, and ought to serve only as warning signals about problems that should be studied by other means. The conclusions drawn from the ADA reporting system may be inaccurate as there was no assurance of an objective decision of "what is a case." Incomplete reports make it difficult to assure a cause-and-effect relationship between a drug and the adverse effect.

Lilly's most significant objection to the use of voluntary ADR reports data was based on the possibility that estolate reactions are reported more frequently than reactions from other erythromycins, in essence, that the reporting is biased. The labeling for the estolate has included information on adverse liver effects since 1961, and two "Dear Doctor" letters concerning the estolate's hepatic effects have been sent to all physicians. The warning was placed in a box in 1974, and an FDA *Drug Bulletin* reiterated the warning. No warnings at all were required for the non-estolate erythromycins until January 1979, however, and these are not boxed warnings. Lilly stated that to assert that these warnings had no effect would be to claim that the entire labeling/warning system is ineffectual.

Lilly stated that just as the number of adverse reactions for the estolate increased after the boxed warning was required in 1973, the number of reactions reported for all erythromycins increased in 1979 and 1980. Three adverse reactions to estolate and four to non-estolate were reported in 1979, and 42 to estolate and 43 to non-estolate were reported in 1980.

Dr. Marcus Reidenberg, Professor of Pharmacology and Medicine, Cornell University Medical College, an individual who spoke at the hearing, noted that any bias against the estolate that is present in the United States would also be present in foreign countries. He also noted that some manufacturers may ascertain a greater fraction of adverse reactions to their products than others. This "ascertainment bias," combined with mandatory reporting by manufacturers, could produce distortions in the data. He suggested the possibility of excluding manufacturers' reports and comparing only the reports of practitioners.

2. *The K–P study.*

a. *Bureau of Drugs' Position.* The Bureau contended that the K–P study, though elegantly conducted, generated insufficient data to allow inference as to the differences in incidence of hepatic reactions due to the various erythromycins. In the study, the investigators reviewed the records of 899 persons who had been given 1,078 courses of estolate treatment and 1,242 patients who had received 2,583 courses of the base, stearate, or ethyl succinate. The investigators found one "probable" estolate-related hepatic reaction and four "possible" non-estolate-related reactions. The Bureau notice the investigators' conclusion that these findings do not allow inference because the adverse effect is so infrequent (estimated to be less than 1 in 500 to 1 in 1,000) that the likelihood of discovering the reaction is low in such a small population.

b. *Lilly's Position.* Lilly contended that many of the problems inherent in data derived from the voluntary ADR reports are absent in data from the K–P study. Lilly stated that the strength of the K–P study lies in the qualifications and experience of the investigators, the use of quality control and standardized procedures, and the accuracy and completeness of the exposure and outcome data. The population at risk was ascertainable—all patients who took either form of erythromycin and belonged to the plan. Therefore, the adequacy of the sample size to find certain differences in treatment may be determined. Lilly believed that the K–P study was large enough to find a difference between treatments if the true difference is 25-fold—that is, if the difference is one adverse reaction per thousand patients (for non-estolate), as compared to 25 adverse reactions per thousand patients (for the estolate). Lilly conceded, however, that the K–P study might not be large enough to detect the differences under consideration in this case—that is, one adverse reaction per thousand patients (for the estolate), compared to 0.04 adverse reaction per thousand patients (for the non-estolate), also a 25-fold difference.

Dr. Reidenberg reviewed his calculation that, assuming a baseline prevalence of one adverse reaction per thousand, a study that could reliably detect a doubling of this prevalence would require the review of 18,000 non-estolate cases and 18,000 estolate cases. He questioned whether the information gained would be worth the cost of such a study.

The firm concluded its discussion of the K–P study by quoting the investigators as saying, "Our study group was too small for us to be able to demonstrate with statistical significance that the cholestatic hepatitis occurred at a greater rate among users of erythromycin estolate than users of the non-estolate forms. Neither can it be concluded from these data that there were no differences."

3. *The Medicaid Studies.*

a. *Bureau of Drugs' Position.* The Bureau stated that the review of Medicaid records is a promising tool for post-market surveillance because of the large number of patients involved, but noted that use of this type of study is still in its infancy. Because of differences in reporting practices, services covered, and refills allowed, it is difficult to compare results among States.

The Bureau found the results of two Medicaid studies to be conflicting with respect to certain age groups. For example, in Texas, hepatic reactions in children under 11, for the estolate and the non-estolate, accounted for 36 percent of all reactions (children and adults). In Michigan, children under 11 accounted for only 8.6 percent of all hepatic reactions. This suggests that the States have different methods of recording diagnoses, that a certain portion of the pediatric population is being missed, or that there is some difference in the tabulation of data between the two States. The Bureau stated that without more information it would be difficult to draw sound conclusions and, therefore, cautioned the Committee against relying too heavily on these data.

b. *Lilly's Position.* Lilly contended that the population at risk in the Medicaid studies is the patients who received either form of erythromycin in the studied States. Lilly asserted that the studies were of sufficient size to demonstrate a one-and-one-half to twofold ratio of risk with high probability. Lilly concluded that the two Medicaid studies are not inconsistent with each other in that both studies indicate similar incidence of hepatic reactions for estolate and non-estolate erythromycins.

4. *Clinical Trials of Hepatic Reactions.*

a. *Bureau of Drugs' Position.* The Bureau presented several prospective clinical trials suggesting that a higher frequency of hepatic dysfunction is associated with the estolate than with other erythromycins. A brief description of the major clinical trials presented follows.

(1) Patients with chronic pustular dermatitis were treated with erythromycin estolate in two series (Ref. 20). The first series included 80 patients; an additional 13 patients were treated in the second series. After 14 to 21 days of therapy, abnormal liver function tests were obtained in 12 percent of the patients in the first series and in 38 percent of the patients in the second series.

(2) The estolate hepatotoxity described in the preceding paragraph, was compared to the hepatotoxicity noted in one patient out of 18 (5 percent) with the stearate (Ref. 21). The investigator also reported that one patient with a history of an hepatic reaction from the estolate had no hepatic dysfunction when treated with the stearate.

(3) Women in the second half of pregnancy received the estolate, clindamycin hydrochloride, or placebo for the treatment of genital mycoplasmal infections (Ref. 1). All pretreatment SGOT levels were normal. Of the 97 women treated with clindamycin hydrochloride, 4 (4.1 percent) developed abnormal SGOT levels. Of the 97 women treated with the estolate, 14 (14.4 percent) developed abnormal SGOT levels. Of the 104 women treated with placebo, 3 (2.9 percent) abnormal SGOT levels. As soon as it was noted that women on the estolate developed a higher rate of abnormal SGOT levels than those taking clindamycin hydrochloride or placebo, incoming patients were given the stearate instead. Of the 97 patients treated with the stearate, 3 (3 percent) developed abnormal SGOT levels.

(4) of 100 patients treated with the estolate for 10 days for acute maxillary sinusitis, 1 patient developed cholestatic hepatitis (Ref. 63).

b. *Lilly's Position.* Lilly reported on six prospective clinical trials investigating hepatic reactins due to the estolate.

(1) No estolate hepatotoxicity was seen in a study of 37 patients. All were given the estolate (Ref. 25).

(2) Twenty-five patients with urinary tract infections were treated with the estolate for two weeks (Ref. 26). The authors report that "no serious toxicity was encountered."

(3) Seventy patients with purulent exacerbations of chronic bronchitis were treated with the estolate for two weeks (Ref. 27). No hepatotoxicity was noted.

(4) There were no liver function test abnormalities in a group of 21 premature infants given the estolate (Ref. 28).

(5) In a comparison of the estolate and penicillin in children, there were no statistical differences between the two groups in elevations of SGOT and bilirubin (Ref. 29).

(6) In an ongoing study of the estolate suspension, ethyl succinate suspension, and penicillin liquid in children with pneumonia, there has been no evidence of hepatotoxicity (Ref. 30).

Lilly reviewed four prospective studies reporting hepatic dysfunction in patients taking the base, stearate, ethyl succinate, or estolate.

(7) Twenty-one patients with cystic fibrosis participated in this study designed to evaluate the relationship of erythromycin prophylaxis and SGOT levels in chronically ill patients (Ref. 31). The authors concluded, "There is no demonstrable effect of erythromycin stearate or erythromycin ethyl succinate upon the SGOT level."

(8) In this study, the SGOT levels of patients receiving the base or the estolate in the treatment of gonococcal urethritis were observed (Ref. 8). The authors report that "abnormal SGOT levels were equally common among patients receiving erythromycin base and the estolate before, during, and after treatment."

(9) In a study of pregnant women given the estolate, the stearate, or placebo, 14.4 percent of the estolate group completing three weeks or more of therapy developed abnormal SGOT levels (Ref. 1; reviewed by the Bureau in paragraph 4.a.(3) above). When the high proportion of abnormal SGOT levels with the estolate was noticed, further incoming patients were given the stearate. Of these patients, 3 percent developed abnormal SGOT levels. Of the patients who received placebo, 2.9 percent developed abnormal SGOT levels.

(10) Patients with chronic pustular dermatitis were treated with the stearate or the estolate (Ref. 21; reviewed by the Bureau in paragraph 4.a. (2) above). Of the first group of estolate patients treated, 12 percent developed hepatotoxicity. Of the second group of estolate patients, 38 percent developed hepatotoxicity. Of the stearate patients, 5 percent developed hepatotoxicity.

Lilly also presented six recently published papers, each reporting one case of hepatic dysfunction due to the ethyl succinate (Refs. 32 through 37).

5. *Other Adverse Reactions.*

a. *Bureau of Drugs' Position.* The Bureau reviewed data on adverse reactions other than those involving the liver obtained from the spontaneous reporting systems of Sweden and the United States. The Bureau found the data to be inconsistent, and no clear conclusions were drawn.

The Bureau studied ADR reports of both gastrointestinal and rash hypersensitivity reactions. These reports of gastrointestinal effects were compared to market share in the same way as reports of hepatic reactions. The Bureau found that the rate of estolate reports in children was 6.7 times greater than that in the non-estolate; in adults, the rate for the estolate was 4.4 times greater than that for the non-estolate. The Bureau noted that some of the gastrointestinal side effects actually may have been subclinical hepatic reactions.

For rash and related effects, the Bureau found that the distribution of reports for the estolate versus the non-estolate tend to approximate the market share in children and adults.

The Bureau presented data from clinical trials which corroborated the inconclusiveness of the ADR reports in regard to gastrointestinal side effects.

(1) The estolate and the base were used in the treatment of gonococcal urethritis (Ref. 8). Of the patients in the base group, 73 percent reported gastrointestinal side effects. Of the patients in the estolate group, 57 percent reported gastrointestinal side effects. The number of patients with vomiting, pain, or moderately severe nausea or diarrhea was 30 percent in the base group and 13 percent in the estolate group.

(2) The base was used in 17 women in the treatment of *Haemophilus vaginalis* (Ref. 22). Therapy was discontinued in four patients due to nausea, diarrhea, and abdominal cramps. Three other patients developed nausea and/or diarrhea, but continued therapy.

(3) Propionyl erythromycin (a closely related forerunner of erythromycin estolate) was given to 134 children and adults who were contacts and carriers of staphylococci and streptococci (Ref. 23). The drug had to be discontinued in six children because of severe vomiting, abdominal cramps, and severe nausea.

(4) In a comparison of the ethyl succinate, stearate, and estolate in streptococcal infections, 156 patients were given the estolate, 102 were given the ethyl succinate, and 47 were given the stearate (Ref. 14). Of eight patients

developing gastrointestinal side effects, seven were in the estolate group. One adult taking the estolate developed loose stools and pruritus ani. Therapy was discontinued in two children taking the estolate because of nausea and abdominal cramps. Another four children treated with the estolate reported nausea, vomiting, abdominal cramps, and diarrhea, but continued therapy. One child treated with the ethyl succinate developed a moderate skin rash and vomiting, but therapy was not stopped.

(b.) *Lilly's Position.* Lilly stated that gastrointestinal side effects are dose-related and less frequent for the estolate than the non-estolate. Because of these side effects, it is usually not possible to increase the dosages of enteric-coated base, stearate, or ethyl succinate to achieve blood and tissue concentrations comparable to those obtained with the estolate.

The firm reviewed four clinical trials investigating gastrointestinal side effects.

(1) Of patients treated with the estolate, 13 percent reported severe to moderately severe effects, while 30 percent of patients treated with non-estolate reported side effects, two stopping treatment (Ref. 8; reviewed by the Bureau in paragraph 5.a.(1) above).

(2) In a study using erythromycin base, 4 of 17 patients stopped treatment because of nausea, abdominal cramping, or diarrhea (Ref. 22; reviewed by the Bureau in paragraph 5.a.(2) above). Three others experienced these side effects but continued treatment.

(3) In a comparative study of they estolate, stearate, and penicillin in treating disseminated gonococcal infections, three of five stearate-treated patients developed nausea and vomiting, therapy was discontinued in one. One of nine estolate-treated patients experienced nausea but continued treatment, while none of the nine penicillin-treated patients vomited or discontinued therapy (Ref. 38).

(4) In a study of 269 patients given the stearate, 33 percent of the patients experienced gastrointestinal disturbance (Ref. 39). Five percent of the patients discontinued treatment because of vomiting, abdominal pain, or diarrhea.

Studies in dogs indicate that erythromycin has a stimulating effect on the smooth muscle and the motility of the intestine (Ref. 40). The firm suggested that this effect might be the cause of the reported nausea, vomiting, and diarrhea. The base, stearate, and ethyl succinate being absorbed to a lesser extent than the estolate may result in higher residual erythromycin concentrations in the bowel lumen, thus causing more gastrointestinal side effects.

Lilly concluded that the lower rate of gastronintestinal effects associated with the estolate may be of clinical significance because physicians often advise that the drugs be taken with food to decrease gastronintestinal disturbances. However, food can interfere with the absorption of non-estolate erythromycins.

6. *In Vitro Data.* Dr. Hyman Zimmerman, Professor of Medicine at George Washington University, appeared at the hearing on behalf of the Bureau. He discussed the significance of biochemical abnormalities, stating that drugs that cause overt jaundice are likely to cause a higher incidence of abnormalities than those that are not associated with overt jaundice (Ref. 24). He referred to a number of in vitro studies conducted with chlorpromazine, which has about a one percent incidence of jaundice, and promazine, which has a very negligible reported rate of jaundice. Observations in Chang liver cells, rat hepatocytes, rabbit liver slices, and perfused liver indicate that chlorpromazine caused significantly more injury. This is consistent with the hypothesis that drugs that produce injury by hypersensitivity can produce injury in in vitro models.

When the estolate was compared with the base in a similar manner, Dr. Zimmerman stated that the estolate, but not the base, led to injury in Chang liver cells in suspension or culture, to suspensions of rat hepatocytes and the isolated, perfused rat liver. Dr. Zimmerman noted that translation of in vitro observations to in vivo phenomena must be made with caution, but in light of the clinical data with which the in vitro observations are consistent, these data are convincing.

*B. Bioavailability*

A summary of the bioavailability data presented by Lilly and the Bureau follows.

1. *Blood Levels of Free Base.* Erythromycin estolate appears in the blood as the total propionyl ester and, through hydrolysis, as free base. FDA's Anti-infective Agents Advisory Committee concluded in 1973 that the estolate is likely to be more effective than other erythromycins because of higher blood levels. However, the data reviewed by the Committee at that time did not distinguish between levels of free base and the levels of propionyl ester obtained. The estolate produces blood levels of total erthromycin three to four times higher than those obtained after administration of the base or stearate.

The Bureau's assertion that the estolate is not more bioavailable than other erythromycins is based on the results of bioavailability studies conducted by the University of Texas in Austin. These studies used as assay method that quantitatively differentiated the free base in presence of the ester.

a. *Bureau of Drug's Position.* The Bureau contended that erythromycin estolate does not possess significant antibacterial activity until it has been hydrolyzed to the base. Therefore, the Bureau asserted that a comparison of the levels of free base obtained with the different erythromycins is more meaningful than a comparison of total erythromycin levels. The Bureau discussed the results of 11 recent studies which compared the bioavailability (as indicated by blood levels) of erythromycin estolate with that of another erythromycin. Bioavailability was determined by newly developed methodology which permitted differentiation between the levels of free base and the particular salt (estolate, stearate, or ethyl succianate).

The Bureau argued that all but one of the studies indicate that, in terms of free base, the estolate is not more bioavailable than other erythromycins: the estolate was equally or less bioavailable. (Although there may be exceptions, it is generally true that if one drug in oral dosage form is 80 to 120 percent as bioavailable as the reference drug in oral dosage form, the two drugs are considered bioequivalent.) A brief description of those studies follows. The bioavailability values given are in terms of free base.

(1) The University of Texas Study—a comparison of estolate and stearate, single-dose, fasting (Ref. 41). The estolate was 45 percent as bioavailable as the stearate. The mean peak concentration for the estolate was 25 percent that obtained with stearate.

(2) The University of Texas Study—a comparison of estolate capsules, enteric-coated base tablets, and stearate tablets, multiple-dose, fasting (Ref. 41). The study employed 24 volunteers in a crossover design. A total of five doses was given every six hours.

After the first dose, the estolate was 36 percent as bioavailable as the base, and 65 percent as bioavailable as the stearate. After the fifth dose, however, there was no difference between the drugs—the estolate was 88 percent as bioavailable as the base and 135 percent as bioavailable as the stearate. Cumulative values (after doses 1, 2, and 5) indicate that the estolate is 66 percent as bioavailable as the base and 96

percent as bioavailable as the stearate. Thus, the estolate is not more bioavailable than the base or stearate.

(3) A comparison of estolate capsules and stearate tablets, single-dose, fasting (Ref. 42). Blood levels were monitored for 12 hours after dose administration. The estolate was 22 percent as bioavailable as the stearate. The mean peak concentration of free base for the estolate was 24 percent that of the stearate.

(4) A comparison of estolate capsules and stearate, single-dose, nonfasting (Ref. 42). The presence of food reduced the bioavailability of the stearate and increased that of the estolate. However, the estolate was still only 89 percent as bioavailable as the stearate. The mean peak concentration for the estolate was only 64 percent that of the stearate.

(5) A comparison of estolate capsules and stearate tablets, multiple-dose, fasting (Ref. 42). A total of five doses was given and blood samples were drawn periodically after the fifth dose for 12 hours. The bioavailability of the estolate was 47 percent that of the stearate. The mean peak concentration was higher for the stearate than for the estolate.

(6) A comparison of estolate capsules and stearate tablets, multiple-dose, nonfasting (Ref. 42). As in the previous study, a total of five doses was given and blood samples were drawn periodically after the fifth dose for 12 hours. The bioavailability of the estolate was found to be 66 percent of the stearate.

(7) A comparison of estolate capsules and enteric-coated base, multiple-dose (Ref. 43). Twelve doses were given to 16 volunteers in a crossover study. A two-hour fast was observed before and after drug administration. Samples were taken until the eighty-fourth hour. The estolate was not shown to be more bioavailable than the base. After the first two doses, the estolate was 90 percent as bioavailable as the base. After doses 9 through 12, the mean cumulative bioavailability of the estolate was 99 percent of the base. After the first and ninth doses the differences in the mean peak concentration was statistically significant in favor of the base. After all other doses, the differences in mean peak concentration were not significant.

(8) A comparison of estolate capsules and enteric-coated base tablets, nonfasting, multiple doses (Ref. 44). A total of 12 doses was given during 72 hours. Blood levels were monitored after doses 1, 2, 9, 10, 11, and 12. The estolate was not shown to be more bioavailable than the base. After the first two doses the bioavailability of the estolate was 109 percent that of the base. After doses 9 through 12, the mean cumulative bioavailability of the estolate was 85 percent that of the base. The mean peak concentration for the base was higher at each measurement than that of the estolate, but was not statistically significant.

(9) A comparison of estolate capsules and ethyl succinate tablets, multiple dose, nonfasting (Ref. 45). This was a two-way crossover study; five doses of each drug were given every six hours. Blood levels were measured at specified intervals for 36 hours. The mean peak concentration after each dose was higher for the ethyl succinate than for the estolate. After the first dose the ethyl succinate was 11 percent more bioavailable than the estolate. After the fifth dose, the estolate was 25 percent more bioavailable than the ethyl succinate. However, the hydrolysis data indicate that after the fifth dose the ethyl succinate was 75 percent hydrolyzed, rather than 50 to 60 percent. On the basis of 75 percent hydrolysis to base, the bioavailability of the estolate was only 6 percent higher than that of the ethyl succinate. The cumulative bioavailability of free base after doses 1, 2, 3, and 5 was 92 percent for the ethyl succinate in comparison with the estolate.

(10) A comparison of estolate capsules and ethyl succinate tablets, multiple dose (Ref. 46). A total of three doses of each drug was given. The first and second doses were given under fasting conditions; the third dose was given 20 to 30 minutes after breakfast. The cumulative bioavailability of the ethyl succinate was 91 percent that of the estolate. Under the nonfasting state of the third dose, the ethyl succinate was 93 percent as bioavailable as the estolate.

(11) A comparison of the estolate suspension and the ethyl succinate suspension, multiple dose, nonfasting (Ref. 47). This was a two-way crossover study using 25 volunteers. Each drug was given every six hours for a total of nine doses. In this study significantly superior blood levels were obtained from the estolate. The bioavailability of the estolate was 296 percent that of the ethyl succinate after the first dose. After the fifth and ninth doses it was 427 percent and 496 percent respectively. The mean peak concentration after the first, fifth, and ninth doses show the same trend.

The Bureau pointed out that 400 mg of the estolate and the ethyl succinate were administered, but that the normal dose of the estolate is only 250 mg while that of ethyl succinate is 400 mg. However, even after normalizing the values of 400 mg dose to 250 mg dose of the estolate, higher blood levels of free base were obtained with the estolate.

b. *Lilly's Position.* Lilly's presentation was aimed at refuting the Bureau's statement in the December 4, 1979 **Federal Register** that "The bioavailability of erythromycin estolate, in terms of free base, is, if anything, poorer than that of other erythromycins tested" and at establishing that the estolate is more reliably absorbed than other erythromycins. Lilly reviewed essentially the same studies presented by the Bureau. The firm's discussion of the studies is described below. The paragraphs referred to are in the Bureau's presentation, above. Unless otherwise noted, bioavailability is in terms of free base.

a. *Blood Levels of Free Base.* (1) Lilly criticized the University of Texas studies (Refs. 55 and 56; described in paragraphs (1) and (2) above as Ref. 41) because they did not include all forms of erythromycin and because they were conducted under fasting conditions. The firm stated that, in practice, erythromycin is often taken with food because the gastrointestinal side effects of all forms are then reduced. In addition, Lilly briefly discussed a clinical trial indicating that the presence or absence of food can greatly influence the bioavailability of erythromycin products (Ref. 57).

In regard to the single-dose University of Texas study, Lilly cautioned, as did the investigator, against drawing conclusions from a single-dose study alone, as it might lead to erroneous conclusions. Lilly also asserted that the variability among subjects was so great that differences in blood levels of free base were not statistically significant.

The firm noted that, in the multiple-dose University of Texas study, both the stearate and the base produced widely variable blood levels of free base between doses, compared with the gradual but steady rise of free base levels obtained with the estolate. In addition, the firm noted that after steady-state conditions were reached, the mean bioavailability for the estolate was greater than that for the stearate, but noted that the investigators concluded that the difference was not statistically significant.

(2) Lilly discussed the multiple-dose study of the estolate capsules with enteric-coated base under nonfasting conditions described in paragraph (7), above (Ref. 43). In that study, patients were administered 12 doses of a drug, one every six hours.

After the first dose on the third day—the ninth dose—the estolate produced

blood levels which were only 73 percent of those of the base. However, over a full day for the four steady-state doses, (doses 9 through 12) the estolate was 99 percent as bioavailable as the base. The firm concluded from this that conclusions drawn from the multiple-dose University of Texas study (in which only five doses were given over the course of the study) would unrealistically favor the base.

(3) In order to determine the relative bioavailability of the estolate under conditions closely related to medical practice, Lilly undertook a study comparing estolate capsules with enteric-coated base in volunteers immediately after meals (Ref. 44; described in paragraph (8), above). As did the Bureau, Lilly concluded that this study demonstrated that the estolate and base are essentially bioequivalent, and noted the large intersubject variability with the base.

Lilly claimed its comparison of this study and the University of Texas studies shows that the variability of blood levels in patients receiving the base increases markedly when it is administered with food. However, with the estolate, blood levels are relatively constant whether or not the drug is taken with food. After the first dose in the Texas study, the percent standard deviation of the serum erythromycin base concentrations was 109 percent (range, 43 to 275 percent) for the base, and 56 percent (range, 38 to 82 percent) for the estolate. Under pseudo-steady-state conditions, this percent standard deviation decreased to 84 percent (range, 44 to 167 percent) for the base, and 36 percent (range, 30 to 47 percent) for the estolate. When the same products were adminstered immediately after meals in the Lilly study, the percent standard deviations of the serum erythromycin based concentration for the first dose of the base was 170 percent (range, 100 to 422 percent) decreasing to 63 percent (range, 35 to 117 percent) under pseudo-steady-state conditions. For the estolate capsule, the percent standard deviation was 69 percent (range, 48 to 83 percent), decreasing under steady state conditions to 40 percent (range, 29 to 51 percent).

(4) Lilly discussed two unpublished studies comparing estolate capsules and ethyl succinate tablets (Ref. 45; described in paragraph (9) and Ref. 46 described in paragraph (10), above). In the first study, patients were given 250-mg capsules of estolate and 400-mg tablets of ethyl succinate. In the second study, patients were given 500 mg of the estolate or 800 mg of the ethyl succinate. In both studies the total erythromycin blood levels for the estolate were two to four times that of the ethyl succinate despite the 60 percent greater dosage of the ethyl succinate. Lilly stated that in the first study the estolate was hydrolyzed to free base to the extent of 23 percent, while the ethyl succinate was hydrolyzed to the extent of 57 percent. In the second study, the blood levels for the estolate were 2.2 times that of the ethyl succinate after the first dose, 3.1 times greater after the second dose, and 2.7 times greater after the third dose. Free base was present in approximately the same proportion.

(5) Lilly presented two studies comparing the estolate oral suspension with the ethyl succinate oral suspension. In the first study (not reviewed by the Bureau) the investigators found that significantly higher concentrations of total erythromycin and the free base were obtained with the estolate than with ethyl succinate when they were administered with food (Ref. 58). Although a greater proportion of the ethyl succinate is hydrolyzed to resulting free base, the free base concentration from the ethyl succinate is only about one-sixth that obtained from the estolate.

The second study of oral suspensions is described in paragraph (11) above (Ref. 47). The firm noted the Bureau's statement that even after normalizing the doses, the levels of free base for estolate were significantly higher than those of the ethyl succinate.

(6) Dr. Charles Ginsburg, Director of Ambulatory Services at the University of Texas, Southwestern Medical School, an individual who appeared at the hearing, reported on several studies he had conducted comparing liquid preparations of the estolate and the ethyl succinate administered with or without milk to children (no citation was given). He emphasized that there are only two liquid preparations of erythromycin available—the estolate and the ethyl succinate. Dr. Ginsburg's data corroborated Lilly's data. The administration of milk did not affect the bioavailability of either drug.

2. *Reliability of Absorption.*

a. *Bureau of Drugs' Position.* The Bureau noted that the intersubject variation in the absorption of the estolate appears to be smaller than that of enteric-coated base. In the multiple-dose, non-fasting study described in paragraph (8) of the Bureau's presentation, above, the coefficient of variation (an indication of intersubject variation) for the base after the first two doses was twice as large as that of the estolate (Ref. 44). After the ninth dose, the coefficient of variation of the base is 15 to 20 percent higher for the base than that of the estolate. Of the 24 patients receiving the base, seven failed to attain measurable blood levels in the first six hours after drug administration. One subject had no measurable blood level for 12 hours following the first dose of the base. All subjects who received the estolate, however, had measurable levels of free base within three hours after the first dose. However, the Bureau stated that there appears to be no clinical advantage to the greater reliability of absorption of the estolate because a patient with an infection so serious as to require immediate blood levels would likely be hospitalized and receiving antibiotics intravenously.

b. *Lilly's Position.* Lilly contended that the estolate is the most reliably and completely absorbed form of erythromycin, with total erythromycin concentrations several times those obtained following administration of other erythromycins. In addition, essentially the same total erythromycin concentrations are obtained when the estolate is administered with or without food and with different volumes of water. Four studies were cited to support these contentions (Refs. 42, 59, 60, and 61).

The absorption of enteric-coated base was said to be highly variable. In a study of fasting subjects administered enteric-coated base every six hours (not reviewed by the Bureau), steady-state blood levels of the drug were generally higher each day after the first and second doses than after the third and fourth doses (Ref. 62). This variability in concentration with time of day was repeatedly observed.

That blood levels obtained with the stearate are variable and influenced by food and fluid was confirmed in the University of Texas study. Lilly quoted the investigators: "Overall, the absorption of erythromycin stearate is markedly decreased when administered shortly after a meal and appears not to be affected if dosing occurs one hour prior to a meal."

3. *Tissue Concentration.*

a. *Bureau of Drugs' Position.* The Bureau reported on three tissue concentration studies: tonsil, aqueous humor, and middle ear exudate (Refs. 48, 49, and 50). Two studies compared the estolate with the ethyl succinate; the aqueous study compared the estolate with the base. In these studies, bioavailability was determined in terms of total erythromycin. The estolate is approximately 20 percent hydrolyzed in vivo, and the ethyl succinate is, on the average, 50 percent hydrolyzed to free

base in vivo. The Bureau, therefore, estimated the levels of free base by dividing the estolate levels by five, and the ethyl succinate levels by two. The Bureau concluded that although the estolate sometimes produced higher tissue levels of free base than other erythromycins, there appeared to be no clinically significant advantage of one erythromycin preparation over another. (See *Clinical Effectiveness* section, below.)

b. *Lilly's Position.* Lilly discussed several tissue concentration studies. Studies of erythromycin estolate concentrations in maxillary sinus exudate and tears were not comparative, and Lilly simply reported the results (Refs. 63, 64, and 65). Lilly also discussed the tonsil tissue, aqueous humor, and middle ear exudate studies presented by the Bureau (Ref. 48 described in Bureau's position above). The firm stated that the higher tonsillar levels for the estolate may have therapeutic implications because in vitro studies show that progressive increases of erythromycin concentrations above the minimum inhibitory concentration for beta-hemolytic streptococci result in an accelerated killing rate.

Dr. Ginsburg reviewed a study in which he found significant differences (in favor of the estolate) between levels of erythromycin obtained from estolate and ethyl succinate liquid preparations in the tears of children (no citation was given). (There were no significant differences in the salivary concentrations between the two drugs.) Dr. Ginsberg suggested that the higher tear levels may be of clinical significance in a diseases of the eye and lung caused by chlamydia in children.

4. *Therapeutic Effect of Propionyl Ester.*

a. *Bureau of Drugs' Position.* The Bureau contended that the propionyl ester has no therapeutic effect other than serving as a reservoir out of which active free base is hydrolyzed.

The Bureau reviewed the results of Lilly's mouse protection studies which compared the effectiveness of intravenously administered propionyl ester and erythromycin base against experimentally induced *Streptococcus pyogenes* infections (Ref. 51). (The drugs were administered intravenously in order to minimize variation due to absorption differences.)

When mice were treated 1 hour post-infection, the median effective dose of the base was 16 mg/kg, while that of the propionyl ester was 24 mg/kg. When treatment was given 2 hours pre-infection, the median effective dose of the base increased to 41 mg/kg, while that of the propionyl ester was 29 mg/kg.

The propionyl ester hydrolyzes into free base at a relatively slow rate (one half-life is 93 minutes). Thus, the Bureau argued that this single dose study is biased in favor of the propionyl ester. In normal treatment of bacterial infections, treatments must be continued for several days or relapse will occur. When the base was given after infection, the protective effect was too short-lived. The greater protection from administration of the propionyl ester was due to the prolonged effect of its continued hydrolysis long after the comparative erythromycin base dosage had been eliminated from the mice's systems.

The Bureau reviewed two in vitro studies which, it claimed, indicate that the propionyl ester is inactive and that any activity in its solutions is proportional to its hydrolysis rate.

(1) Five of the 2' esters of erythromycin were ranked in order of hydrolysis (Ref. 52). The ester with rapid hydrolysis performed with full activity as soon as it was applied to growing cultures. The propionyl ester had a slow onset of bacteriostatic activity coinciding with its slow hydrolysis rate.

This study also evaluated the ability of various erythromycin esters to inhibit radio-labeled erythromycin from binding to ribosomes. (It is through ribosomal binding that erythromycin exerts its bacteriostatic effect by inhibiting protein synthesis.) The propionyl ester was unable to displace significant amounts of the labeled erythromycin from the ribosomes—the amount of binding by the esters was proportional to their hydrolysis rates.

(2) That the antimicrobial effect of the estolate is due to hydrolysis of the propionyl ester to free base was urged by the Bureau to have been demonstrated by a second study comparing bactericidal effects at different pH levels (Ref. 53). There was a very slow and gradual appearance of activity from the propionate solutions at pH unfavorable for hydrolysis (pH 6.0). There was, however, a rapid and complete appearance of anti-bacterial activity at a favorable hydrolytic pH (pH 7.5).

The Bureau contended that there is no direct evidence of hydrolysis taking place after the propionyl ester is absorbed by bacterial cells. Strong indirect evidence, however, points to lack of hydrolysis within cells.

An unpublished study indicates, by use of radioactive tracers, that the propionyl ester is absorbed into bacterial cells to a much greater extent than is erythromycin base (Ref. 54). The Bureau stated that if the ester were hydrolyzed to an active form intracellularly, the ester would show much higher activity than the base in vitro studies. It does not.

Finally, the Bureau cited Lilly's attempts to find bacterial esterases capable of splitting the estolate. The firm was able to find esterases capable of splitting ester complexes other than the propionyl ester of erythromycin. Thus far, the search for enzymes capable of splitting the propionyl erythromycin ester within the bacterial cell has been unsuccessful.

b. *Lilly's Position.* Lilly contended that the propionyl ester has a therapeutic effect in addition to its providing a reservoir from which the base is continously hydrolyzed. It argued that the ester configuration modifies the chemical, physical, and biological characteristics of erythromycin and increases its lipid solubility. This facilitates its penetration into macrophages and tissues. Thus, the ester acts as both a reservoir and a delivery system of erythromycin.

Lilly stated that if a significant amount of the propionyl ester enters the bacterial cell and intracellular hydrolysis occurs, then an antibacterial effect should be observed. Lilly reviewed the studies evaluated by the Bureau indicating that the propionyl ester is accumulated intracellularly to a great extent than the base (Ref. 54). The firm noted that techniques have not yet been developed for determining actual intracellular hydrolytic activity. However, because there has not yet been found a medium in which the propionyl ester is not hydrolyzed to free base, it can only be assumed that the estolate within cells is a source of active free base.

Lilly reviewed studies which indicate that the uptake of antibiotics by alveolar macrophages is related to lipid solubility—the more lipid-soluble drugs being concentrated to a greater extent than the non-lipid-soluble drugs (Refs. 67 and 68). At 1 minute, the concentration of the estolate was 17 times that of the base, at 15 minutes, the difference was six times; and at 1 hour, the ester concentrations were twice that of the base. The firm suggested that this characteristic might be significant in difficult-to-treat infections caused by viable intracellular bacteria such as Legionnaire's disease and *Chlamydia trachomatis.*

Lilly reported on the mouse protection study comparing the effectiveness of intravenously administered propionyl ester and erythromycin base against experimentally induced *Streptococcus*

*pyogenes* infections (Ref. 51; reviewed by the Bureau above).

The median effective dose for the propionyl ester was higher than that for the base. However, chromatographic analysis indicates that the amount of active free base hydrolyzed from the propionyl ester was significantly less than the median effective dose of the base. Thus, Lilly argued that the propionyl ester itself appears to have provided the requisite additional antimicrobial activity. These results were confirmed in a second mouse protection study performed in mice infected with *S. pyogenes* and *S. aureus* (Ref. 69, noted reviewed by the Bureau).

*C. Clinical Effectiveness*

1. *Streptococcal Pharyngitis and Tonsillitis (strep throat).* The recommended children's dose for the ethyl succinate, the stearate, and the base is 30 to 50 mg/kg/day in the treatment of streptococcal pharyngitis. In 1978, the recommended dose for the estolate in the treatment of streptococcal pharyngitis in children was changed from 30 to 50 mg/kg/day to 20 to 50 mg/kg/day based on data submitted by Lilly (Ref. 118).

a. *Bureau of Drugs' Position.* The studies submitted by Lilly to support the labeling change investigated only the estolate. Other studies (described below) indicated that higher doses of the ethyl succinate suspension are as effective as lower doses of the estolate suspension. The difference in dosage amount is not very great and appears to be of little clinical significance as there appear to be no adverse effects (i.e., gastroinstestinal) from higher doses of the ethyl succinate. In addition, there is no difference in effectiveness between low doses of the estolate capsules (23 mg/kg/day) and comparable doses of the stearate tablets (23.1 mg/kg/day) (Ref. 14—described below).

(1) Erythromycin estolate was used successfully in the treatment of children at a dosage of 20 mg/kg/day (Ref. 70). This study made no comparison with other erythromycins.

(2) In a comparison of the estolate and the ethyl succinate in children, eradication rates were similar in both groups (Ref. 16). The dosage of the ethyl succinate was 40 mg/kg/day, while that of the estolate was 20 mg/kg/day. The effectiveness of the ethyl succinate at lower doses was not studied.

(3) This study compared two dosage schedules of the ethyl succinate oral suspension with penicillin in oral suspension (Ref. 13). One regimen of the ethyl succinate was the usually recommended dosage (44 to 50 mg/kg/day) while the other was below the usual recommended dose (27.5 to 33.4 mg/kg/day). There was no significant difference between the results of penicillin and the higher, usually recommended, dose of the ethyl succinate.

The higher dosage of the ethyl succinate was then compared with penicillin and the estolate given below the usual recommended dose (10 to 20 mg/kg/day) and at the usual recommended dose (20 to 50 mg/kg/day). There seemed to be no difference in the effectiveness of the estolate and the ethyl succinate when both were given at the recommended dose. The authors concluded that the dosage of the ethyl succinate should be above 39.5 mg/kg/day, but that the estolate was as effective as penicillin at 16.5 mg/kg/day in patients under 45.4 kg.

(4) This study compared ethyl succinate suspension (51.4 mg/kg/day) and the estolate suspension (31.8 mg/kg/day) (Ref. 14). The cure rate for the ethyl succinate was 97.9 percent, while that of the estolate was 93.3 percent.

In the same study, the investigators compared ethyl succinate chewable tablets (38.7 mg/kg/day) with estolate chewable tablets (38.3 mg/kg/day). The cure rate of the ethyl succinate was 90.9 percent, while that of the estolate was 95.7 percent.

A third comparison was made in the same study, between stearate tablets (23.2 mg/kg/day) and estolate capsules (23.0 mg/kg/day). The cure rate for the stearate was 100 percent; that of the estolate was 95.8 percent.

b. *Lilly's Position.* Lilly reviewed the studies reviewed by the Bureau indicating that the estolate is effective in the eradication of streptococcal microorganisms at 15 to 20 mg/kg/day (Refs. 13, 14, 16, and 70).

Dr. Ginsburg presented preliminary results of an ongoing study comparing the effectiveness of the estolate (15 mg, twice daily) to the ethyl succinate (15 mg, twice daily) in the treatment of strep throat (Ref. 120). The author stated that no study had compared the effectiveness of the ethyl succinate with the effectiveness of the estolate when both were given at the lower dose at which the estolate is effective. It is essential to determine whether the ethyl succinate may also be effective at the lower doses. Of the 100 patients studied so far, 52 were given the estolate with an 11-percent failure rate. Of the 48 patients given the ethyl succinate, there was a 31-percent failure rate.

2. *Primary Syphilis.*

a. *Bureau of Drugs' Position.* No comparative studies of the effectiveness of the estolate and other erythromycine have been conducted. (The only studies have been of re-treatment rates. These studies clearly cannot demonstrate effectiveness.) Thus, the Bureau stated that it cannot be determined whether the estolate is more effective than othe erythromycins.

(1) This study investigated the re-treatment rates of different dosages of erythromycin estolate in the treatment of primary syphilis (Ref. 71). One year after treatment, the re-treatment rate for the 10 g schedule was 35 percent, while that of the 15 to 20 g schedule was 15 percent. Based on this study, the Public Health Service recommends 10 days of orally administered erythromycin in a total dosage of 20 g. The recommendation does not specify a particular form of erythromycin.

(2) This study compared the 12-month re-treatment rates of 20-g schedule of erythromycin base and and 30-g schedule of the base (Ref. 12). A 25-percent re-treatment rate was obtained with a 20-g schedule, while a 9.9-percent re-treatment rate was obtained with the 30-g schedule. The authors concluded that erythromycin base in a total of no less than 30 g for 10 days is an acceptable alternative to penicillin in the treatment of early syphilis.

b. *Lilly's Position.* Lilly submitted no additional studies on the effectiveness of erythromycin on the treatment of primary syphilis.

3. *Haemophilus influenzae Otitis Media.*

a. *Bureau of Drugs' Position.* The Bureau claimed that superior effectiveness of the estolate over the ethyl succinate cannot be seen from the available data. None of the studies compares erythromycin estolate with other erythromycin.

(1) The Bureau reviewed the results of two studies, which Lilly had in combining them, claimed showed that the estolate is more effective than the ethyl succinate in the treatment of *H. influenzae* otitis media (Ref. 72). In the first study, there was a cure rate of 77 percent with an ethyl succinate/sulfonamide combination, and a 50-percent cure rate with ethyl succinate alone. In the second study, there was a cure rate of 88 percent with an estolate/sulfonamide combination and an 81-percent cure rate with the estolate alone. The Bureau argued that the effectiveness of different drugs should be compared only when they are used in the same study.

(2) Contrasting results were obtained in another study comparing an estolate/sulfonamide combination and the estolate alone (Ref. 73). In this study, a 95-percent cure rate was obtained with the estolate/sulfonamide combination,

but only 63 percent of the patients treated with the estolate alone were cured.

(3) The investigators compared the effectiveness of an estolate/sulfonamide combination, and the estolate alone, among others (Ref. 74). They stated, "This study shows that the fixed combination of erythromycin estolate and triple sulfonamide suspenion is as effective in acute otitis media as the single drug ampicillin and more effective than the ingredients of the combination used separately."

(4) In another study, the effectiveness of erythromycin ethyl succinate/sulfonamide suspenion was compared with the effectiveness of the ethyl succinate alone, as well as with several other drugs (Ref. 75). The authors concluded that ampicillin, penicillin with sulfonamide, and erythromycin ethyl succinate/trisulfapyrimidine were the most bactericidal treatment.

(5) In still another study, the investigators compared the erythromycin concentration in middle ear exudate following estolate or ethyl succinate administration in eight patients with otitis media (Ref. 49). The concentration in the ethyl succinate group ranged from 0.24 to 1.02 mcg/mL with a mean of 0.84 mcg/mL. The concentration in the estolate group ranged from 1.68 to more than 8 mcg/mL, with a mean of 4.18 mcg/mL. The higher levels obtained with the estolate appear to be of little clinical significance as the patient with the highest serum and middle ear exudate levels of erythromycin had a moderate grouth of *H. influence* on the culture.

b. *Lilly's Position.* Lilly reviewed the results of the study comparing the ethyl succinate and an ethyl succinate/sulfonamide combination and its own study comparing the estolate and an estolate/sulfonamide combination (Ref. 72; described in the Bureau's paragraph (1) above). It was urged that, taken together, the studies indicate that the estolate is at least as effective in *H. influenzae* otitis media as a combination of the ethyl succinate and a sulfonamide.

4. *Diphtheria.*

a. *Bureau of Drug's Position.* The Bureau was aware of no data showing superior effectiveness of the estolate over other forms of erythromycin in the treatment of diphtheria.

(1) Many references to erythromycin therapy in diphtheria do not specify a particular form of the drug. The Report of the Committee on Infectious Diseases of the American Academy of Pediatrics (1977) states, under treatment of diphtheria, "Antimicrobial therapy is a valuable adjunct, but it is not a substitute for antitoxin. Penicillin and erythromycin are the drugs of choice." The Bureau cited nine other published articles generally recommending erythromycin in the treatment of diphtheria (Refs. 76 through 82, 115, and 119).

(2) Diphtheria carriers were treated with benzathine penicillin, erythromycin estolate, or clindamycin (Ref. 83). All treatments were successful; 92 percent of the patients in the estolate group had negative cultures at the end of treatment.

(3) Diphtheria carriers were treated with erythromycin estolate for 6 days (Ref. 84). All carriers with positive throat cultures before therapy developed negative cultures during therapy. Two weeks after the end of therapy, however, 21 percent of the patients had positive cultures again.

(4) This was a discussion of treatment in the 1970 diphtheria epidemic in San Antonio (Ref. 85). Children from 2 to 5 years old received erythromycin lactobionate intravenously or the ethyl succinate intramuscularly for 3 days, followed by the stearate for 4 days. Patients 6 years old and over received the lactobionate intravenously for 3 days and the stearate for the next 4 days. *C. diphtheriae* was eliminated from all patients.

Carriers were treated with estolate syrup for 7 days. There was a success rate of 89 percent.

(5) Of 142 carriers treated with procaine penicillin, 14 did not have the organism eliminated from the nasopharynx (Ref. 86). The patients who did not respond to penicillin were then given erythromycin ethyl succinate, which eliminated the organism in every patient.

(6) The Bureau reported on five published articles reporting on the successful use of erythromycin other than the estolate ethyl carbonate in the treatment of diphtheria (Refs. 87 through 91).

b. *Lilly's Position.* Lilly reviewed two literature excerpts (Refs. 83 and 84; reviewed by the Bureau in paragraphs (2) and (3) above) reporting on the estolate's effectiveness in eradicting diphtheria bacilli. The firm noted that other erythromycins have not been studied in the treatment of diphtheria.

5. *Pertussis.*

a. *Bureau of Drugs' Position.* The Bureau stated that there is no published evidence that one form of erythromycin is more effective than another in the treatment of pertussis (whooping cough).

(1) The Bureau reviewed nine excerpts from the medical literature which recommend erythromycin for the treatment of patients with pertussis or exposed to pertussis (Refs. 76, 78, 80, 92 through 96, and 115). No specific form of erythromycin is recommended.

(2) Erythromycin estolate eradicated *B. pertussis* from the nasopharynx in 2 to 7 days (Ref. 97). In the no antibiotic group, the organism was eliminated in 7 to 14 days. The estolate had no effect on the duration or severity of the disease, as judged by the length of hospitalization.

(3) All 131 patients treated with the estolate had negative nasopharyngeal cultures on the sixth day of treatment (Ref. 98). On the same day, 11 to 36 patients treated with ampicillin still had positive cultures.

(4) In an outbreak of pertussis, 200 patients (including 17 carriers) were treated with the ethyl succinate (Ref. 99). At the end of treatment, 118 patients (59 percent) were cured, and 62 (31 percent) were greatly improved. After 1 week of treatment, all 17 carriers had negative cultures.

(5) In this study patients received erythromycin as the ethylcarbonate or the stearate for 4 to 21 days (Ref. 100). The author simply noted that erythromycin seems to have prophylactic value in preventing or aborting whooping cough.

b. *Lilly's Position.* Lilly stated that eradication of *Bordetella pertussis* from the nasopharyngeal secretions of patients is important in reducing the occurrence of secondary cases and bacterial complications. In one study (Ref. 97; reviewed by the Bureau in paragraph (2) above) estolate treatment was superior to no treatment in reducing the length of time that nasopharyngeal cultures remain positive for *B. pertussis.*

Lilly asserted that the recent addition of the *B. pertussis* indication in the labeling of all erythromycin products was based on studies conducted only with the estolate. Through a freedom of information request, Lilly learned that the recommendation that the indication be approved was based on a review of published reports. Lilly asserts that only three of the published reports provided dosage information and identified the specific erythromycin product (Refs. 97, 98 and 99; reviewed by the Bureau in paragraphs (2), (3), and (4) above). Two of those three publications reported that the estolate was effective at a dosage of 40 to 50 mg/kg/day.

The third excerpt was a report of clinical experience with the ethyl succinate at a dose of 30 mg/kg/day. Lilly asserts that approval of the pertussis indication could not have been based on this study because, as stated by the reviewing medical officer, "It is not written in this paper how

evaluations of 'cured,' 'greatly improved' etc. were made . . . by the evaluation of clinical signs, duration of the disease or bacteriological results."

Lilly reported on a more recent excerpt stating that 7 days of ethyl succinate therapy at a dosage at 55 mg/kg/day failed to eradicate *B. pertussis* from an infant (Ref. 125; not reviewed by Bureau). A second infant who was exposed to the first patient contracted pertussis in spite of prophylactic use of ethyl succinate suspension at the same daily dose. The authors emphasized the need for further study.

6. *Legionnaire's Disease.*

a. *Bureau of Drug's Position.* The Bureau stated that different erythromycin preparations have been used in the treatment of Legionnaire's disease, but that data showing one erythromycin to be more effective than another were not available.

(1) The Bureau reviewed three literature excerpts recommending erythromycin for the treatment of Legionnaire's disease (Refs. 101, 102, and 115). Two of the articles recommend no specific type of erythromycin. One article states that the estolate should not be used because of the risk of hepatotoxicity.

(2) In this study, 15 of 16 patients treated with the lactobionate (intravenous) or stearate had a satisfactory response to therapy including seven who were administered immunosuppresive therapy concurrently (Ref. 99). One patient was not initially diagnosed as having Legionnaire's disease and was treated with penicillin, ampicillin, gentamycin, and oxacillin. He died on the tenth day of illness after receiving only two doses of erythromycin.

b. *Lilly's Position.* In severe infections or in patients with compromised host defenses, parenteral erythromycin therapy is often used in hospitalized patients. However, Lilly stated that in the management of outpatients with pneumonia that may be Legionnaire's disease, the use of an oral erythramycin product is recommended.

Studies in Detroit have demonstrated a lack of response to the stearate in spite of oral doses of 4 g or more daily (Refs. 121 and 122 not reviewed by the Bureau). One patient developed the disease while receiving the drug. Intravenous erythromycin at similar does resulted in therapeutic response.

Investigators at the University of Vermont also have emphasized the unpredictability of the stearate form in the initial treatment of Legionnaire's disease (Ref. 123; not reviewed by the Bureau).

Dr. Dolin, Professor of medicine at the University of Vermont, an individual who appeared at the hearing, noted that Legionnaire's disease is one of the few clinical situations in which erythromycin is the initial treatment of choice for a life-threatening infection.

Dr. Dolin stated that reliable absorption is a paramount consideration in selection of any oral therapy for a life-threatening disease. He reiterated the concern that absorption of oral erythromycin preparations other than the estolate is highly erratic and unreliable, particularly when taken without regard to meals, as is usually the case. He stated that he had observed several cases of Legionnaire's disease that progressed on oral base therapy, which eventually reponded to intravenous erythromycin therapy in the hospital.

Dr. Dolin stated that there are other properties of the estolate which suggest that it may have potential advantages in the treatment of Legionnaire's disease. Although it is argued that the propionyl ester is inactive, it is clear that significant antibacterial activity is associated with the ester and that hydrolysis to free base occurs continuously. In addition, the ester appears to achieve preferential penetration and concentration in macrophages, which are an important site of replication for Legionella organisms.

7. *Chlamydial Infections.*

a. Bureau of Drugs' Position. The Bureau stated there are no data demonstrating that one erythromycin is more effective than another in the treatment of chlamydial urethritis. In addition, the Bureau stated that there are no data demonstrating that one erythromycin is more effective than another in the treatment of chlamydial conjunctivitis or chlamydial pneumonia in neonates.

(1) Two literature excerpts recommend erythromycin (without specifying a particular form), to treat chlamydial pneumonia and chlamydial conjunctivitis (Refs. 105, 106, and 115).

(2) For chlamydial pneumonia, the authors suggest the use of systemic erythromycin, without specifying a particular form (Ref. 105). They suggest the use of systemic erythromycin ethyl succinate to treat chlamydial neonatal conjunctivitis.

(3) The Bureau reviewed two excerpts describing the successful use of the ethyl succinate in chlamydial pneumonia in children. (Refs. 107 and 108).

(4) A patient with chlamydial pneumonia who was treated unsuccessfully with other antibiotics responded well when the lactobionate was administered for 3 days, followed by the ethyl succinate for another 10 days (Ref. 109).

(5) Oral erythromycin estolate or topical erythromycin ointment was given to 36 infants with chlamydial conjunctivitis (Ref. 110). Of those patients, 35 had negative cultures on the seventh day. The systemic erythromycin was effective in eradicating *C. trachomatis* from the nasopharynx of six patients.

(6) This study compared the incidence of chlamydial infections in infants born to mothers with treated and untreated *C. trachomatis* cervical infections (Ref. 111). There was no infection among the infants of the 10 treated mothers treated with the base. Of the 20 infants born to untreated mothers, however, 6 developed chlamydial conjunctivitis, 2 developed chlamydial pneumonia, and 1 developed an asymptomatic nasopharyngeal infection.

b. *Lilly's Position.* Lilly stated that comparative studies of the estolate, base, and tetracycline in the treatment of nongonococcal urethritis due to *Chlamydia trachomatis* and/or *Ureaplasma urealyticum* were in progress (Ref. 124; not reviewed by the Bureau). There is not evidence that tetracycline resistance has been developing in strains of *U. urealyticum.* Therefore, it is important to establish which form of erythromycin will provide statisfactory alternate therapy.

8. *Campylobacter Enteritis.*

a. *Bureau of Drugs' Position.* The Bureau stated that there are no data comparing the effectiveness of the erythromycins in the treatment of campylobacter enteritis.

(1) Five literature excerpts recommed erythromycin treatment, but no particular form of erythromycin is specified (Refs. 112 through 116).

(2) Most of 37 children with campylobacter enteritis recovered spontaneously on conservative therapy (Ref. 117). However, seven children were treated with the estolate for relapse or persistent signs and symptoms of disease. Stool cultures became negative within 48 hours. Symptoms disappeared in five of the seven patients within 24 hours.

b. *Lilly's Position.* Lilly submitted no other data on the effectiveness of the estolate in camphylobacter enteritis.

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## V. Committee's Conclusions and Recommendations

On July 28, 1981, the Ad Hoc Advisory Committee on Erythromycin Estolate submitted written responses to the ten issues included in the February 27, 1981 notice of hearing. Some of the issues were modified by the Committee. The Committee responses are summarized below.

Before reaching specific issues, the Committee passed two resolutions: (1) "On the basis of available data, it is the conclusion of this Committee that no convincing evidence has been brought forward to indicate that the use of erythromycin estolate in children is associated with a higher incidence of cholestasis than other erythromycin formulations. As far as efficacy is concerned, the evidence clearly indicates that erythromycin estolate is as effective as other erythromycin formulations." (2) "The Committee finds the data available on erythromycin estolate hepatotoxicity adequate to estimate a risk of approximately one case per thousand exposures, but totally inadequate to determine the risk of other forms of erythromycin in adults. Serum levels with the estolate, whether evaluated as total drug or erythromycin base, are at least as good as with other dosage forms. Theoretical advantages of the estolate, such as superior tissue levels, penetration into alveolar macrophages, and perhaps initially more reliable absorption and bioavailability when the drug is taken with food (as is most likely in clinical practice) have been raised. These considerations lead the Committee to the conclusion that there is indeed a reason for the continued availability of the erythromycin estolate and the exercise of clinical judgment in evaluating the risk/benefit ratio of the particular erythromycin formulation to be used in each individual patient."

### *A. Adverse Reactions*

The Committee concluded that the incidence of hepatotoxicity for adults was greater for erythromycin estolate than for other erythromycins. The Committee concluded that the difference in the incidence of hepatotoxicty is of clinical concern.

The Committee unanimously voted that the incidence of hepatotoxicity in children was not greater for the estolate than for other erythromycins. Accordingly, the Committee made no finding on the clinical significance of the difference.

The Committee also found that the Bureau's voluntary adverse reaction reports to date did not determine the relative incidence for erythromycin adverse liver effects.

The Committee unanimously found that the data presented from the K–P study to date cannot reliably be used to determine the incidence of adverse liver effects for erythromycins. The Committee made no finding on the clinical significance of differences shown. The Committee unanimously found that a useful historical cohort study could be devised.

The Committee answered the question "Did the data presented from prospective clinical studies provide a reliable determination of the incidence of adverse liver effects for erythromycins?" by a vote of one positive, five negative, and five abstentions. The discussion preceding the vote indicates a concern over the conflicting results of the prospective clinical studies.

The Committee unanimously concluded that there are no major differences between erythromycin estolate and other oral erythromycins in the incidence of adverse effects in adults or in children, other than those involving the liver. One committee member described "no major difference" as the situation where there was a difference in one study in one direction but there is a slight difference in another study in the opposite direction.

### *B. Bioavailability*

The Committee unanimously concluded that it could not determine whether tissue concentration studies of the estolate and the ethyl succinate provide any evidence of a clinically significant advantage for adults or children because there is no valid interpretation of the clinical significance of bioavailability of the propionyl ester in tissue.

The Committee concluded that studies showing observable higher blood levels of erythromycin as the estolate indicate that the estolate is more reliably absorbed than other erythromycins. The Committee unanimously found, however, that it did not know whether blood levels of the estolate are related to the therapeutic response. It considered the ability of a medication to be taken without regard to meals as a clinical advantage.

The Committee unanimously agreed that all except one of the bioavailability studies in adults reviewed by the Bureau of Drugs demonstrate that blood levels of the base obtained following administration of erythromycin estolate are at least equal to those obtained after administration of erythromycin base, stearate, and ethyl succinate. For children, the unanimous response was that the erythromycin estolate suspension provides consistently higher blood levels measured as the base than does ethyl succinate suspension.

The Committee unanimously concluded it could not determine whether the propionyl ester of erythromycin estolate, apart from its being hydrolyzed, contributes to the therapeutic effect of erythromycin estolate. Accordingly, the Committee did

not determine whether the contribution of the propionyl ester to the therapeutic effect was of clinical significance.

The Committee unanimously concluded that a prospective study to determine the therapeutic effect of the propionyl ester may be needed. However, because such a study is not technically feasible at the present time, the Committee did not determine what the design of the study should be.

*C. Clinical Effectiveness*

The Committee concluded that erythromycin estolate has not been shown by means of randomized clinical trials to offer greater therapeutic effectiveness in adults over other erythromycins. The Committee also concluded that there is suggestive evidence that in some clinical circumstances erythromycin estolate may show therapeutic advantage in children over other erythromycins.

The Committee unanimously concluded as follows, "In the treatment of streptococcal pharyngitis in children, erythromycin estolate has been shown to be effective at a lower dose than that recommended for all other erythromycins. An ongoing prospective randomized clinical study shows superiority of the estolate over the ethyl succinate at 30 mg/kg/day given only twice a day. The lower dose and the less frequent dosing constitute a clinical advantage." The Committee made no findings on the effectiveness of various erythromycins in the treatment of primary syphilis.

The Committee unanimously concluded that neither erythromycin estolate nor erythromycin ethyl succinate is recommended alone for the treatment of *H. influenza* otitis media and that there have been no randomized, controlled clinical trials to show whether erythromycin estolate has any advantage over other erythromycins in the treatment of diphtheria, pertussis, Legionnaires' disease, chlamydial infections, or *Campylobacter* enteritis.

*D. Risk/Benefit Determination*

The Committee determined that the risk/benefit ratio of the estolate in adults is favorable, referring to the previously accepted resolution pertaining to adults. The Committee determined that the estolate has a favorable risk/benefit in children and referred to the previously accepted resolution pertaining to children. The Committee unanimously recommended two possible changes in labeling for adult dosage forms: (1) The wording "further, the propionyl ester contributes to the activity of the drug through additional hydrolysis to the base at the bacterial cellular level" should be deleted from the labeling, and (2) indications of other infections, such as *Chlamydia trachomatis* and *Campylobacter*, should be added if data were submitted to support the added indications. The Committee also discussed whether the indications for chronic use, such as prophylaxis of rheumatic fever, should be removed, but took no vote on this issue.

The Committee recommended that the boxed warning in pediatric dosage forms of the estolate should have "ADULTS" juxtaposed to "WARNING". This would indicate that the data at this time do not justify a boxed warning for pediatric uses. The Committee unanimously recommended that the labeling changes suggested for the adult dosage forms be included in the pediatric dosage forms as well: (1) That the sentence stating that the estolate is hydrolyzed at the bacterial cellular level be deleted from the labeling; and (2) that indications for *Chlamydia trachomatis* and *Campylobacter* infections be considered as the data are submitted.

**VI. Comments on the Committee's Report**

The agency received three comments on the Committee's report—one each from HRG, the American Medical Association and Lilly.

1. HRG stated that the evidentiary findings of the Committee support the Bureau's arguments that erythromycin estolate tablets and capsules are unsafe, and that this requires the revocation of provisions for certification. In particular, HRG cites the findings of the Committee that greater hepatotoxicity is associated with the estolate and that this is of clinical concern.

Next, HRG stated that under the act, evidence of effectiveness must consist of adequate and well-controlled clinical investigations, citing *Weinberger* v. *Hynson, Westcott, and Dunning*, 412, U.S. 609, 629–630 (1972). HRG then asserted that the only benefits of the estolate over other erythromycins identified by the Committee were "theoretical . . . such as superior tissue levels, penetration into alveolar macrophages and perhaps initially more reliable absorption and bioavailability when taken with food." Finally, HRG argued that unless there are adequate and well-controlled clinical investigations showing greater benefits from the estolate than from other erythromycins, the agency is required by law to revoke the provisions for certification of the estolate tablets and capsules.

HRG urged the Commissioner to disregard the Committee's recommendation that the estolate remain on the market, stating that this issue is outside the Committee's mandate (none of the ten questions posed asked whether the estolate should remain on the market) and expertise. HRG maintained that it is only the Committee's factual findings, which it contended support revocation of certification provisions, that should be given weight in the Commissioner's deliberations.

HRG is correct that the Committee was not directly asked whether erythromycin estolate tablets and capsules should remain on the market. It was believed that the Committee's judgment on that issue would be clear from the answers to the ten questions posed. However, as the Committee's recommendation that the estolate remain on the market summarizes its risk/benefit evaluation, the Commissioner believes it proper for him to consider that recommendation in making his decision.

The Commissioner disagrees that the data presented compel the conclusion that the estolate has an unfavorable risk/benefit ratio. The Commissioner concludes that it is likely that the estolate is associated with hepatotoxicity to a greater extent than are other erythromycins. However, as explained in the following section, the Commissioner also finds benefits to offset this risk.

Moreover, the Committee concluded that available data tend to suggest benefits of the estolate compared to other erythromycins. The Committee's statements about the relative risks must be considered in this context. From the Committee's recommendation that the estolate be allowed to remain on the market, it clearly recognized that the crucial issue here is a weighing of risks and benefits, not an evaluation of the risks taken in isolation.

HRG misapplies the legal requirement that effectiveness must be demonstrated by adequate and well-controlled clinical investigations. Substantial evidence of the estolate's effectiveness was established at the time of its approval, and was not questioned in this proceeding. While the act requires proof of effectiveness derived from adequate and well-controlled clinical trials for pre-market approval, it makes no such requirement for safety evaluations. This is significant because this action fundamentally has been an inquiry into whether the risks of the estolate outweigh the benefits to such an extent that the certification provisions should be revoked on grounds of lack of safety. The effectiveness of the estolate is

relevant only insofar as it demonstrates sufficiently superior benefits over other erythromycins to offset the postulated greater risks of the estolate. In this type of consideration, data that are not derived from adequate and well-controlled clinical trials are not precluded from consideration.

In addition, the Commissioner disagrees with HRG that the only benefits associated with the estolate are theoretical. The Commissioner agrees with the Committee's conclusion that "the ability of a medication to be taken without regard to meals [is] a clinical advantage." On the other side of the scale, the Commissioner concludes that under conditions of actual use, the estolate is not less bioavailable than the other erythromycins as stated in the proposal. Thus, the benefits of the estolate are at least equal to the benefits of the other erythromycins.

2. The American Medical Association expressed its concern over the agency's "increasing tendency to evaluate both approved and new drugs on the basis of 'relative' safety and efficacy." It also argued that the agency should take no action against a drug unless controlled studies and experience demonstrate that a drug is not safe or effective. On the basis of the data presented, the Association concluded that the hepatotoxicity associated with the estolate is not of sufficient clinical significance and incidence to warrant revocation of provisions for certification, regardless of the estolate's bioavailability.

The Commissioner agrees that revocation of provisions for certification of erythromycin estolate tablets and capsules is not justified at this time. It must be emphasized however, that the act places the burden of proving the safety and effectiveness of a drug on those persons wishing to market it. Thus, the act does not require the agency to wait until a marketed drug is proven unsafe or ineffective before taking regulatory action but, rather, requires it to withdraw approval when there is evidence to suggest that a drug may no longer be considered safe and effective.

Further, as explained above, this matter is fundamentally an inquiry into the safety of the estolate, and the safety of any drug must be considered in the context of other drugs indicated for the same conditions. In a safety determination, the "relative efficacy" of a drug is relevant only insofar as it offsets the drug's risks, which otherwise may be considered unacceptable.

3. Lilly contended that the Committee reconfirmed its prior position that the estolate has a favorable risk/benefit ratio and should remain available for use. The company believed that the estolate had not been shown to be associated with a higher incidence of adverse hepatic effects, and that, because of its more reliable absorption, superior bioavailability, and better penetration of tissues and infection sites, the estolate offered important therapeutic advantages over other erythromycins. The firm recommended the prompt rescission of the proposal to revoke provisions for certification.

The Commissioner has concluded that revocation of certification provisions is not warranted at this time. The basis for this conclusion is set forth below.

## VII. Commissioner's Conclusions, Labeling

The Commissioner has evaluated all the data presented, weighing the risks and benefits of the estolate against the risks and benefits of other erythromycins. He has considered the recommendations of the Committee. The Commissioner accepts the Committee's recommendations that the adult and pediatric dosage forms of erythromycin estolate are safe, and that revocation of the certification provisions would be unjustified. In addition, he will take no action regarding the pediatric dosage forms. Accordingly, the December 4, 1979 proposal is withdrawn and the request made in HRG's petition is denied. The basis for the Commissioner's conclusion follows.

1. *The Risks.* In 1973, the Commissioner concluded that hepatotoxicity is associated only with the estolate. The data presented in this review of the estolate's safety indicate that all forms of erythromycin, adult and pediatric dosage forms, are associated with hepatotoxicity to some extent. Thus, the hepatotoxicity associated with the estolate may be of less significance than was thought in 1973, as it is now known that all forms of erythromycin can cause hepatotoxicity.

The Commissioner further concludes that the risk of hepatic reactions from any form of erythromycin in adults and children is quite small. In the Kaiser-Permanente study, for example, after examining the results of 3,661 courses of erythromycin therapy, the investigators were able to identify only one "probable" case and four "possible" cases of erythromycin-related hepatotoxicity.

The Commisssioner is unable to determine from the data presented in this proceeding the precise relative incidence of hepatic reactions caused by the various erythromycins. Although data obtained from the Bureau's ADR reporting system may be a useful post-marketing tool to estimate the relative incidence of adverse reactions in some cases, such estimates are imprecise in the present case. Lilly has raised the possibility of bias in the reporting of reactions resulting from the warnings in the labeling, "Dear Doctor" letters, and FDA *Drug Bulletins*. The Bureau's analysis of cases of hepatotoxicity, while demonstrating an approximate 25-fold greater number of cases in adults associated with the estolate than with other forms of erythromycin, cannot exclude the possibility that some or much of this difference is due to a reporting bias rather than to a true difference in adverse reaction rates. Neither can this reported 25-fold difference be dismissed on the basis of evidence offered by Lilly; the criticism that the data are flawed by a reporting bias is potentially valid but nevertheless is itself speculative and unproven. Thus, while an accurate estimate of the relative incidence of hepatic reactions associated with the various erythromycins cannot be made from the ADR reports, the Commissioner agrees with the Advisory Committee that the incidence of hepatotoxicity in adults is greater for the estolate.

Similarly, the reports of unnecessary surgery to relieve hepatic distress not known to be caused by the estolate could be subject to the same type of bias. There is no way to estimate the frequency of surgery to relieve hepatic distress actually caused by, but never attributed to, other erythromycins.

The examination of Medicaid data is a promising tool for post-marketing surveillance, and the Commissioner encourages its use. However, further analysis into the recordkeeping differences among States and the recordkeeping practices within a State under consideration must be conducted before inferences drawn can be relied upon.

Other data presented support the conclusion that the incidence of hepatic reactions is greater for the estolate than for other erythromycins. While none of the prospective clinical trials of hepatic reactions presented studied nearly enough patients to determine the actual incidence of cholestatic hepatitis, in many of the studies abnormal liver function tests were obtained from significantly more estolate patients than from non-estolate patients.

In addition, the in vitro data presented by Dr. Zimmerman were supportive. The data indicate that the estolate, but not the base, causes injury to Chang liver cells in suspension or culture, to suspensions of rat hepatocytes, and to isolated, perfused rat liver. The

Commissioner recognizes the difficulties inherent in applying in vitro data to in vivo phenomena. However, as with the abnormal liver function tests, the Commissioner believes that use of such data as supporting evidence is appropriate.

2. *The Benefits.* In 1973, the Commissioner concluded that the estolate was more bioavailable than other erythromycins. The estolate's greater bioavailability in comparison to other erythromycins was thought to result in comparable clinical effectiveness at lower doses in the treatment of streptococcal pharyngitis and primary syphilis. In 1981, the advisory committee also concluded that the estolate's lower dose and less frequent dosing in the treatment of streptococcal pharyngitis in children constitute a clinical advantage of the estolate.

The Commissioner does not agree with either the 1973 conclusion or the current committee's conclusion that the estolate is more effective than other erythromycins in the treatment of streptococcal pharyngitis. When proper dosages are used the cure rates of all the erythromycins are similar. The fact that lower doses of the estolate can be used would be considered a benefit only if fewer adverse effects were associated with lower doses, but this has not been shown. The data on gastrointestinal side effects are contradictory and no conclusions can be drawn from them. As explained above, the incidence of hepatic reactions are greater for the estolate than for other erythromycins.

The Commissioner disagrees with the previous finding regarding primary syphilis. The studies on which the conclusion that the estolate is more effective was based examined 12-month re-treatment rates, rather than microbiological effectiveness at the end of treatment. It is obvious that a number of factors other than treatment effectiveness will affect the re-treatment rate. No other data on the effectiveness of the various erythromycins in treating syphilis were presented in this proceeding. Thus, the Commissioner concludes that no difference among erythromycins in the treatment of syphilis has been shown.

Data intended to demonstrate the greater effectiveness of the estolate in the treatment of Legionnaire's disease were also presented. However, these data were not comparative, and no conclusions can be drawn from them. The Commissioner is aware that a comparative study of Legionnaire's disease is ongoing, but whether a clinical advantage for the estolate will be shown cannot, of course, be determined at this time.

In addition, data on diphtheria, pertussis, chlamydial infections and campylobacter enteritis were presented. These data are inconclusive and inadequate to demonstrate an advantage of one erythromycin over another.

Further, the Commissioner disagrees with both the 1973 conclusion that the estolate is more bioavailable than other erythromycins as well as the Bureau's assertion in 1979 that in terms of free base, the estolate is less bioavailable than other erythromycins. Studies presented by the Bureau in this proceeding indicate that under fasting conditions the estolate achieves significantly lower blood levels than other erythromycins, particularly in the first doses. These studies also indicate, however, that under nonfasting conditions, in terms of free base, the solid dosage forms of the various erythromycins are essentially bioequivalent. The Commissioner acknowledges that in actual practice, drugs are often taken with meals. Thus, there is no evidence of any additional benefit, or any additional disadvantage, accruing to the estolate because of its bioavailability.

There has been no dispute that in terms of free base, the estolate suspension is significantly more bioavailable than the ethyl succinate suspension. No clinical benefit has been shown to result.

At this time, no conclusions can be drawn concerning the tissue levels of free base. It has not been demonstrated that the various erythromycins are hydrolyzed to free base in tissue to the same extent that they are in the blood. Thus, it is not clear that higher tissue levels of free base are in fact obtained with the estolate. Further, there has been no demonstrated clinical advantage to the presumed higher tissue levels.

In addition, the data presented are inadequate to determine the validity of the theory that the propionyl ester acts as a delivery system to the bacterial cell as well as functioning as a reservoir out of which free base is hydrolyzed. Similarly, at this time there are no data demonstrating that the propionyl ester is in fact hydrolyzed to free base within bacterial cells and alveolar macrophages.

The lack of greater clinical effectiveness or greater bioavailability does not lead to the conclusion that there are no greater benefits associated with the use of the estolate. The greater benefit is due to the estolate's reliability of absorption.

The Bureau and Lilly both stated that the estolate is more reliably absorbed initially than the base when taken with food. In addition, Lilly noted that the investigators in the University of Texas studies concluded that the absorption of the stearate is decreased when it is taken shortly after a meal. The Committee concluded, and the Commissioner agrees, that the estolate's reliable absorption when taken with food is a clinically significant advantage that cannot be overlooked, particularly in potentially fatal diseases, such as Legionnaire's disease. This characteristic of the estolate is quite striking when compared to the absorption of the base under non-fasting conditions—7 out of 24 patients failed to obtain any blood level whatsoever for 6 hours after drug administration. Free base from the estolate was present in all estolate patients three hours after drug administration. (It must also be noted that the ethyl succinate's absorption is unaffected by food.)

3. *Risk/Benefit Determination.* The Commissioner concludes, as in 1973, that the risk/benefit ratio of erythromycin estolate, in both adult and pediatric dosage forms, is favorable. Thus, the Commissioner disagrees with the Bureau's 1979 assertion that the estolate has an unfavorable risk/benefit ratio.

The risk of hepatotoxicity is greater from the estolate than from other erythromycins, but the actual risk of any one patient incurring an hepatic reaction is quite small. Further, the reaction, though unpleasant, has never resulted in a fatality.

The Bureau asserted that the estolate is less bioavailable than other erythromycins. The Bureau had tentatively concluded that this, taken with the greater hepatotoxicity associated with the estolate, was sufficient to unfavorably alter the risk/benefit ratio. The Commissioner now concludes that the erythromycins are essentially bioequivalent. Thus, while the bioavailability of the estolate compared to other erythromycins cannot be counted as a benefit as in 1973, neither can it be considered a detriment.

Similarly, the clinical effectiveness of the estolate compared to other erythromycins cannot be considered either a risk or a benefit. The data presented demonstrate no differences among the various erythromycins in clinical effectiveness.

The clearly demonstrated benefit of estolate administration is its reliable absorption when taken with food. This is of particular benefit in serious diseases. Thus, the Commissioner concludes that the estolate's relatively greater risk of hepatotoxicity is offset by its relatively greater reliability of absorption.

The data presented in this proceeding have been set forth in detail. They are voluminous and conflicting. The Commissioner believes, however, that the data support the continued marketing of the estolate, which will allow practitioners to select the most appropriate drug for each individual patient.

4. *Labeling.* Labeling changes are set forth in a related document published elsewhere in this issue of the **Federal Register**. The changes are explained in this notice for information purposes.

The Committee recommended that the pediatric dosage form (oral suspension, chewable tablets, and pediatric drops) of the estolate juxtapose the word "ADULTS" and "WARNING" above the black box warning. This would indicate that the warning box applies to adults only, not to children. The Commissioner disagrees with this recommendation because data were presented indicating that hepatic reactions do occur in children. The risk of hepatic reactions in children has been known for some time to be far smaller in children than in adults. The data presented at this hearing do not justify any change in the boxed warning. Thus, no change in the current boxed warning is required.

The Committee also recommended deletion from the labeling of all dosage forms the wording "(f)urther, the propionyl ester contributes to the activity of the drug through additional hydrolysis to the base at the bacterial cellular level." The Commissioner agrees. No data demonstrating that the propionyl ester is hydrolyzed at the bacterial cell level were presented.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 201(n), 502, 507, 52 stat. 1041, 1050–1051 as amended, 59 stat. 463 as amended, (21 U.S.C. 321(n), 352, 357)) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1: see 46 FR 26052; May 11, 1981)).

Dated: May 18, 1982.

**Arthur Hull Hayes, Jr.,**

*Commissioner of Food and Drugs.*

[FR Doc. 82-14162 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

### Office of Assistant Secretary for Housing—Federal Housing Commissioner

### 24 CFR Part 203

**[Docket No. R-82-979]**

### Mutual Mortgage Insurance and Rehabilitation Loans

*Corrections*

In FR Doc. 82-12792 appearing on page 20149 in the issue of Tuesday, May 11, 1982; on page 20151, make the following changes:

(1) In column one, § 203.264(b), fifth line, "after" should read "before".

(2) In column three, the third bold face heading now reading "**§§ 203.275 through 203.309 [Removed]**". should read "**§§ 203.305 through 203.309 [Removed]**".

BILLING CODE 1505-01-M

## DEPARTMENT OF THE INTERIOR

### Office of Surface Mining Reclamation and Enforcement

### 30 CFR Part 906

### Abandoned Mine Land Reclamation Program

**AGENCY:** Office of Surface Mining Reclamation and Enforcement (OSM), Interior.

**ACTION:** Receipt of the Abandoned Mine Land Reclamation (AML) Grant Application from the State of Colorado.

**SUMMARY:** On April 29, 1982, the State of Colorado submitted to OSM its proposed abandoned mine land reclamation grant application under the Surface Mining Control and Reclamation Act of 1977 (SMCRA). OSM is seeking public comment on the adequacy of the State grant application. The grant will not be approved until the Secretary has approved the Title IV Reclamation Program.

**DATES:** Written comments on the application must be received on or before 5:00 p.m. June 24, 1982.

**ADDRESSES:** Copies of the full text of the proposed Colorado grant application are available for review during regular business hours at the following location: Office of Surface Mining Reclamation and Enforcement, New Mexico State Office, 219 Central Avenue, NW., Suite 216, Albuquerque, New Mexico 87102.

Written comments shoud be sent to: Robert H. Hagen, State Director, New Mexico State Office, 219 Central Avenue, NW., Suite 216, Albuquerque, New Mexico 87102.

**FOR FURTHER INFORMATION CONTACT:** Robert H. Hagan, State Director, New Mexico State Office, 505/766-1486, Same address as above.

**SUPPLEMENTARY INFORMATION:** On February 16, 1982, a State reclamation plan was submitted to the Secretary. The Colorado Plan is presently being reviewed by the Secretary. Under section 405(f) of the SMCRA, the Secretary cannot approve a State AMLR program grant unless that State has an approved State AMLR program pursuant to section 405(d) of the SMCRA.

On April 29, 1982, OSM received an AMLR grant application from the State of Colorado.

Title IV of the Surface Mining Control and Reclamation Act of 1977 (SMCRA), Public Law 95-87, 30 U.S.C. 1201 *et seq.*, establishes an AMLR Program for the purposes of reclaiming and restoring land and water resources adversely affected by past mining. This program is funded by a reclamation fee imposed upon the production of coal. Lands and water eligible for reclamation under the program are those that were mined or affected by mining and abandoned or left in an inadequate reclamation status prior to August 3, 1977, and for which there is no continuing reclamation responsibility under State and Federal law.

Each State having within its borders coal mined lands eligible for reclamation under Title IV of SMCRA may submit to the Secretary a State reclamation grant application to implement the provisions of the approved State Reclamation Plan. However, grants for reclamation may be issued only to States with an approved Title V Regulatory Program for active mine reclamation and an approved Title IV Reclamation Program. The grant application received from the State of Colorado will be reviewed and held pending a final approval by the Secretary on the State's Title IV program in accordance with SMCRA.

This notice describes the nature of the proposed projects and sets forth information concerning public participation in the development of the projects. This publication does not represent any decision by the Secretary on the Title IV Reclamation Program, but is published solely for the purpose of expediting the review process and the implementation of the reclamation program if the Title IV program of the State of Colorado is approved.

All written comments must be mailed or hand carried to the State Director's Office above.

The Director has found that the State has given the public adequate notice and opportunity to comment in public hearings, and the record of such hearings does not reflect major unresolved controversies.

The comment period will close at 5:00 p.m. on June 24, 1982. Comments received after that time may not necessarily be considered. During the comment period representatives of the State Director's office will be available to meet between 8:00 a.m. and 4:00 p.m. at the request of members of the public to receive their advice and recommendations concerning the proposed State AMLR grant application.

Persons wishing to meet with representatives of the State Director's office during this time period may place such request with Robert H. Hagen, State Director, telephone 505/766-1486 at the State Director's office above.

Meetings may be scheduled at the State Director's Office between 9 a.m. and noon and 1 p.m. and 4 p.m. Monday through Friday excluding holidays.

OSM intends to continue to discuss the State's application with representatives of the State throughout the review process.

In order to comply with the requirements of the National Environmental Policy Act, OSM will assess the environmental effects of all State reclamation projects. The primary basis for this assessment will be the environmental information provided in the project grant application.

The Colorado AML Reclamation Grant Application can be approved if:

1. The Director finds that the public has been given adequate notice and opportunity to comment, and the record does not reflect major unresolved controversies.

2. Views of other Federal agencies have been solicited and considered.

3. The application meets all the requirements of the OSM, AMLR program provisions and the required Federal circulars.

4. The State has an approved regulatory program and an approved State reclamation plan.

The following constitutes a summary of the contents of the submission:

1. Designation of authorized State Agency to administer the program,

2. Objectives and need for the assistance,

3. Project ranking and selection,

4. Coordination with other reclamation programs,

5. Results and benefits expected,

6. Plan of action pertaining to the scope,

7. Monthly or quarterly projections of accomplishments to be achieved,

8. Kinds of data to be collected and maintained,

9. Criteria used to evaluate the results and success of the projects,

10. Key individuals to be employed,

11. Precise location of the project and area to be served,

12. Budgetary calculations for each project,

13. Description of the public's participation in planning and preparation of the grant application,

14. A complete environmental assessment for each project.

Reclamation projects included in application and location:

*El Paso County*

McFerran Project (McFerran Shaft)

*Huerfano County*

Gordon Project (Old Gordon Mine)
Solar Project (Solar Mine)

*Las Animas County*

Royal Project (Royal, Brodhead and Green Canyon Mines)
Cokedale Project (Cokedale Mine airshaft)

*Fremont County*

Bassick Project (Bassick, Mohawk, Florence Canyon, Beacon and Liberty Mines)
Wolf Park Project (Royal Gorge (Thorton) shaft and Royal Gorge #2 Mine)
Coal Creek Project (Bluff Springs and Falgien Mines)

*Delta County*

States Project (States, Independent, Western Star and Green Valley Mine sites)

*Routt County*

Oak Creek Project (Hayden #3 and #4 Mine shafts; Juniper, Edna and Milner strip mines)

*Park County*

Como Project (Como West and King Coal Mines)

*Jefferson County*

Virginia Project (Virginia Mine)

**List of Subjects in 30 CFR Part 906**

Coal mining, Intergovernmental relations, Surface mining, Underground mining.

Date: May 20, 1982.

**J. S. Griles,**

*Acting Director, Office of Surface Mining.*

[FR Doc. 82-14233 Filed 5-24-82; 8:45 am]
BILLING CODE 4310-05-M

## INTERSTATE COMMERCE COMMISSION

### 49 CFR Part 1207

**[Docket No. 38837]**

### Review of Accounting Rules for Class I and II Common and Contract Motor Carriers of Freight

**AGENCY:** Interstate Commerce Commission.

**ACTION:** Advance notice of proposed rulemaking; request for comments.

**SUMMARY:** The Interstate Commerce Commission is reviewing the accounting rules for class I and II common and contract motor carriers of freight (49 CFR Part 1207). The purpose of this review is to identify revisions necessary to make the accounting system more responsive to the Commission's data requirements.

**DATES:** Written responses should be filed with the Commission by June 30, 1982.

**ADDRESSES:** Responses should be mailed to: Bryan Brown, Jr., Bureau of Accounts, Interstate Commerce Commission, Washington, D.C. 20423.

**FOR FURTHER INFORMATION CONTACT:** Thomas Carter, (202) 275-6755.

**SUPPLEMENTARY INFORMATION:** To assist in this review we are requesting carriers to submit their recommendations for revisions. The zone of consideration for this project includes the definitions, instructions, and account texts. Respondents should feel free to recommend consolidation or expansion of account groups, elimination of accounts, and addition of new accounts. Respondents are also requested to suggest revisions to the instructions if they are not clear enough or to recommend additional instructions.

**List of Subjects in 49 CFR Part 1207**

Motor carriers, Uniform system of accounts.

[FR Doc. 82-14174 Filed 5-24-82; 8:45 am]
BILLING CODE 7035-01-M

**49 CFR Part 1244**

**[Ex Parte No. 385 (Sub-No. 1)]**

## ICC Waybill Sample, Revisions

**AGENCY:** Interstate Commerce Commission.

**ACTION:** Notice of meeting in proposed rulemaking proceeding.

**SUMMARY:** The Interstate Commerce Commission published in the Federal Register on February 10, 1982, at 49 FR 6040, a proposed rule to amend 49 CFR 1244 by revising the ICC rail waybill sample. A meeting is to be held to discuss the multiple car, trainload and unit train definitions (shown in item 21 of Appendix A of the rulemaking), as well as alternate definitions and their ability to differentiate the important cost factors in multiple car traffic for use in the Uniform Rail Costing System. No other matters in this rulemaking will be discussed.

**ADDRESSES:** Proposals and notices should be sent to: Office of Transportation Analysis, Room 4126, Interstate Commerce Commission, 12th and Constitution Avenue NW., Washington, D.C. 20423.

The meeting will be held in Hearing Room C at the above address.

**FOR FURTHER INFORMATION CONTACT:** Sidney Fine, (202) 275-7220.

**SUPPLEMENTARY INFORMATION:** Each party interested in participating in the meeting should send written notice to the Commission that it will attend, including names of individuals who will take part in the discussion.

We request that the railroads, as well as any of the other interested parties, submit proposed definitions with reasons why each party feels its definitions are superior or more feasible than those shown in item 21 of Appendix A of the rulemaking. All parties submitting definitions or modifications to the proposed definition shall be prepared to discuss and defend their proposals at the meeting.

**DATES:** Proposals of definitions, and notices to participate in the meeting must be received by June 24, 1982.

The meeting will be held at 9:30 a.m. on June 28, 1982.

**Agatha L. Mergenovich,**

*Secretary.*

[FR Doc. 82-14199 Filed 5-24-82; 8:45 am]

BILLING CODE 7035-01-M

**DEPARTMENT OF THE INTERIOR**

**Fish and Wildlife Service**

**50 CFR Part 17**

## Endangered and Threatened Wildlife and Plants; Proposed Deregulation of Blue Pike

**AGENCY:** Fish and Wildlife, Service, Interior.

**ACTION:** Proposed rule.

**SUMMARY:** The U.S. Fish and Wildlife Service proposes to remove the blue pike (*Stizostedion vitreum glaucum*) and the longjaw cisco (*Coregonus alpenae*) from the U.S. List of Endangered and Threatened Wildlife. This action is based on a review of all available data which indicates that these species are extinct. Blue pike populations declined in the late 1950's and never recovered with the last confirmed specimens taken in the 1960's. Historically, this subspecies was found in Lakes Erie and Ontario, and the Niagara River. Intensive surveys by the Fish and Wildlife Service and States where the species occurred, have failed to yield any additional specimens. In a 1977 survey, the Blue Pike Recovery Team contacted all Fish and Game agencies in the U.S. in an effort to determine if blue pike existed in their waters. After all responded negatively, the Blue Pike Recovery Team concluded that the blue pike was extinct and recommended removing it from the U.S. List of Endangered and Threatened Wildlife.

The longjaw cisco is one of several closely related species of ciscos which occur in the Great Lakes. It was known to occur in Lakes Michigan, Huron, and Erie. Despite the considerable effort of the Service's Great Lake Fishery Laboratory and States around the Great Lakes, there has been no reported collection of this species in U.S. waters since 1967. Recent research has indicated that some species of ciscos in the Great Lakes may constitute hybrid populations. The Fish and Wildlife Service believes *Coregonus alpenae* is extinct and should be deregulated.

**DATES:** Comments from the public must be received by July 26, 1982. Comments from Governors of affected States must be received by August 23, 1982.

**FOR FURTHER INFORMATION CONTACT:** Mr. Robert F. Johnson, Jr., U.S. Fish and Wildlife Service, Federal Building, Fort Snelling, Twin Cities, Minnesota 55111.

**ADDRESSES:** Comments and materials concerning this proposal should be sent to the Regional Director, U.S. Fish and Wildlife Service, Federal Building, Fort Snelling, Twin Cities, Minnesota 55111. Comments and materials received will be available for public inspection by appointment during normal business hours by contacting the Region's Endangered Species staff at the above address.

**SUPPLEMENTARY INFORMATION:**

Background. Blue pike were abundant in the commercial fishery of the late 1800's but by 1915 landings began to fluctuate extensively. Production peaks in excess of 10,000 metric tons occurred in 1915, 1936, 1944, and 1949 and lows under 2,500 metric tons occurred in 1917-19, 1929, 1941, and 1946-47 before the fishery collapsed in 1958. During the past 10 years, the blue pike has been reported to be extinct by several fishery biologists.

Fishery biologists have evidence that an over-intensive fishery, which disrupted self-stabilizing mechanisms within the population, led to the extreme fluctuations and ultimate crash of the fishery. Since young-of-the-year blue pike inhabited the same areas as older members of the populations, they were vulnerable to cannibalism. It has been postulated that overfishing for adults caused unusual numbers of young-of-the-year to escape predation. This would lead to a short population explosion followed by several years of poor recruitment due to over-predation by abundant older fish on the young. An intensive fishery would cause increased amplitude in the fluctuations because the fish would be taken even when they were scarce. In addition, competition with and predation by the newly arrived rainbow smelt, which occupied the same habitat for part of the year, were likely detrimental to this species.

The last successful year-class occurred in 1954 and there was virtually no recruitment to the fishery after that year. Production continued at high levels for another 3 years and then collapsed. As growth rates in this period increased enormously, immature fish were readily exploited which further reduced spawning potential.

The reasons for the collapse of the fishery in 1958 have not been well defined. Summer oxygen deficiencies in the hypolimnion of the central basin probably forced the blue pike into the deeper waters of the eastern basin of Lake Erie where they were more vulnerable to an extensive fishing effort. It has also been suggested that introgressive hybridization with walleye may have been responsible for the final disappearance of the remnant stock.

The longjaw cisco, originally described in 1924, was indigenous to the Great Lakes basin and occurred only in Lakes Michigan, Huron, and Erie. The

longjaw cisco was one of several species of deepwater ciscos utilized by the smoked fish trade and was a very important species in the fishery of the Great Lakes. It was also an important prey species for lake trout and burbot before these fishes were decimated by the sea lamprey. The longjaw cisco has not been seen in Lakes Erie and Huron since the late 1950's. The most recent collection of this species in Lake Michigan was in 1967.

The ciscos, including the longjaw cisco, supported a substantial fishery until about 1950. These fishes were caught exclusively by gillnets set in deep (100–300 feet) water. As the deep water ciscos became scarce, the smaller shallow water species entered the fishery. The cisco or chub fishery of the Great Lakes ceased to exist before 1960 and presently only one cisco, the bloater (*Coregonus hoyi*), is important in the commercial fishery.

The decline of the longjaw cisco and the cisco fishery in general is usually attributed to fishery and environmental problems. The history of the cisco fishery in the Great Lakes is one of increasing exploitation and decreasing stocks. As the ciscos decreased in abundance, there was an increase in the fishery effort along with a decrease in net mesh size. This resulted in further depletion of cisco stocks. In addition to the increased fishing pressure, predation by the sea lamprey and degradation of the habitat further reduced cisco populations. In recent years, problems by hybridization between some species of ciscos has contributed to this decline.

Section 4 of the Endangered Species Act of 1973, as amended, directs the Secretary of the Interior to conduct, at least once every 5 years, a review of all species included in the list of Endangered and Threatened species to determine if any such species should be removed from the list or be changed in status from Endangered to Threatened or Threatened to Endangered. The longjaw cisco was listed in 1967 and the blue pike in 1970 and an official review of their status was initiated in 1979. The lack of recent collections indicates that these species have apparently become extinct. Based on this information, the Service proposes to deregulate the longjaw cisco and blue pike.

## Summary of Factors Affecting the Species

Section 4(c) of the Endangered Species Act (16 U.S.C. 1531 seq.) directs the Secretary to review, at least once every 5 years, all listed species to determine if any species may be delisted or be eligible for a change in status. As part of this review the influence of the five factors listed in Section 4(a) of the Act must be considered. These factors and their effects on the blue pike and longjaw cisco are as follows:

### Blue Pike

1. *Present or Threatened Destruction, Modification, or Curtailment of its Habitat or Range.* Pollution and oxygen depletion may have contributed to the decline of this species.

2. *Overutilization for Commercial, Sporting, Scientific, or Educational Purposes.* Selective fishing by commercial interests may have been a factor in the disappearance of the blue pike.

3. *Disease or Predation.* Predation on adults by the sea lamprey may have contributed to the decline of the species.

4. *The Inadequacy of Existing Regulatory Mechanisms.* The absence of regulations sufficient to protect the fishery may have contributed to the decline of the blue pike.

5. *Other Natural or Manmade Factors Affecting Its Continued Existence.* Competition with rainbow smelt may have been one of the factors contributing to the decline of this species.

Although the exact cause of the disappearance of the blue pike is not known, it appears that the aforementioned factors were major contributing influences.

### Longjaw Cisco

1. *Present or Threatened Destruction, Modification, or Curtailment of Its Habitat or Range.* The longjaw cisco was historically recorded from Lakes Michigan, Huron, and Erie. There have been no known adverse effects on the cisco from water quality degradation or habitat elimination in Lakes Huron and Michigan. Extensive industrial and municipal wastes that contributed to an overall deterioration of water quality in Lake Erie may have led to the decline in the cisco population there.

2. *Overutilization for Commercial, Sporting, Scientific, or Educational Purposes.* An intensive commercial fishery for large ciscos in Lakes Michigan and Huron may have contributed to the decline of *Coregonus alpenae* in these lakes.

3. *Disease or Predation.* Sea lamprey predation in Lakes Michigan and Huron may account for a portion of the longjaw cisco's decline.

4. *The Inadequacy of Existing Regulatory Mechanisms.* The absence of regulations sufficient to maintain the fishery may have contributed to the decline of this species.

5. Other Natural or Manmade Factors Affecting Its Continued Existence. Competition with smaller ciscos, as well as with alewife *(Alsoa pseudoharengus)* and rainbow smelt *(Osmarus mordax)*, was a suspected contributory factor in the decline of the longjaw cisco. Hybridization with other cisco species may also have been a contributing factor in the species' disappearance.

## Effects of this Proposal if Published as a Final Rule

Deregulation of the blue pike and longjaw cisco would result in the removal of these species from the U.S. List of Endangered and Threatened Wildlife. Federal agencies would no longer be required to consult with the Secretary to insure that any action authorized, funded, or carried out by them would not jeopardize the continued existence of the blue pike and longjaw cisco or result in the destruction or adverse modification of their habitat. Restrictions on taking of this species would no longer apply.

## Effect Internationally

The blue pike and longjaw cisco are listed in Appendix I of the Convention of International Trade in Endangered Species of Wild Fauna and Flora. Promulgation of this proposal as final rule may influence their removal from Convention's protection.

## National Environmental Policy Act

A draft Environmental Assessment was prepared in conjunction with this proposed rule. It is on file in the Regional Office, U.S. Fish and Wildlife Service, Federal Building, Fort Snelling; Twin Cities, Minnesota 55111, and may be examined by appointment during regular business hours. This assessment is the basis for a decision that this is not a major Federal action which would significantly affect the quality of the human environment within the meaning of Section 102(2)(C) of the National Environmental Policy Act of 1969 and 40 CFR Parts 1500–1508.

**Note.**—The Department of the Interior has determined that this in not a major rule and does not require preparation of a Regulatory Impact Analysis under Executive Order 12291. The Department has also determined, in accordance with the Regulatory Flexibility Act, that this rule will not have a significant economic effect on a substantial number of small entities. The Service is not aware of negative impacts on small entities from the delisting.

## Primary Author

The primary author of this proposed rule is Mr. Robert F. Johnson, Jr., U.S. Fish and Wildlife Service, Twin Cities, Minnesota,

**Public Comments Solicited**

The Director intends that the rules finally adopted be as accurate and effective as possible. Therefore, any comments or suggestions from the public, other concerned governmental agencies, the scientific community, industry, private interests, or any other interested party concerning any aspect of this proposed rule are hereby solicited. The Service particularly requests comments on the following: (1) Biological or other relevant data concerning any blue pike and longjaw cisco populations which may still exist and (2) additional information concerning the historical range and distribution of this species.

Also, the Service is requesting information on environmental and economic impacts and effects on small entities (including small businesses, small organizations, and small governmental jurisdiction) that would result from the delisting of these species. This information will aid the Service in complying with the requirements of the National Environmental Policy Act, Executive Order 12291 on Federal Regulation, and the Regulatory Flexibility Act, and in preparing any required analyses of effect.

All comments and additional information received will be considered by the Director in the promulgation of a final rule.

**List of Subjects in 50 CFR Part 17**

Endangered and threatened wildlife, Fish, Marine mammals, Plants (agriculture)

**Regulation Promulgation**

**PART 17—ENDANGERED AND THREATENED WILDLIFE AND PLANTS**

Accordingly, it is proposed that part 17, Subchapter B of Chapter I, Title 50 of the U.S. Code of Federal Regulations be amended as follows:

**§ 17.11 [Amended]**

1. Section 17.11 is amended by removing the following from the List of Endangered and Threatened Wildlife:

Cisco, longjaw (*Coregonus alpenae*)
Pike, blue (*Stizostedion vitreum glaucum*)

Dated: April 15, 1982.

**G. Ray Arnett,**

*Assistant Secretary for Fish and Wildlife and Parks.*

[FR Doc. 82-14202 Filed 5-24-82; 8:45 am]

BILLING CODE 4310-55-M

**DEPARTMENT OF COMMERCE**

**National Oceanic and Atmospheric Administration**

**50 CFR Part 658**

**Shrimp Fishery of the Gulf of Mexico; Fishery Management Plan Amendment**

**AGENCY:** National Oceanic and Atmospheric Administration (NOAA), Commerce.

**ACTION:** Availability of plan amendment.

**SUMMARY:** The Assistant Administrator for Fisheries has approved Amendment 2 to the Fishery Management Plan for the Shrimp Fishery of the Gulf of Mexico (FMP), announces its availability, and requests comments on the amendment. This amendment provides an update of the economic information in the FMP. There is no change in regulations associated with the amendment.

**DATE:** Written comments on the plan amendment must be received on or before July 9, 1982.

**ADDRESS:** Comments should be sent to Jack T. Brawner, Acting Regional Director, Southeast Region, National Marine Fisheries Service, 9450 Koger Boulevard, St. Petersburg, Florida 33702. Copies of the fishery management plan amendment are available from Mr. Brawner.

**FOR FURTHER INFORMATION CONTACT:** Jack T. Brawner, 813-893-3141.

**SUPPLEMENTARY INFORMATION:** The Fishery Management Plan for the Shrimp Fishery of the Gulf of Mexico (FMP) was approved May 29, 1980, under authority of the Magnuson Fishery Conservation and Management Act. Final regulations implementing the FMP were published in the **Federal Register** on May 20, 1981, at 46 FR 27489. The Gulf of Mexico Fishery Management Council prepared and submitted for approval Amendment 2 to the FMP. This amendment was approved on April 21, 1982. No regulatory changes will be proposed to implement this amendment.

The amendment provides an update of the economic information in the FMP. Since the preparation and approval of the FMP, the economic condition of the shrimp fishery has undergone significant changes; this amendment provides more recent data. The Council does not believe, however, that the changed conditions require any alteration of the management measures for the fishery.

Dated: May 19, 1982.

**Robert K. Crowell,**

*Deputy Executive Director, National Marine Fisheries Service.*

[FR Doc. 82-14238 Filed 5-24-82; 8:45 am]

BILLING CODE 3510-22-M

# Notices

Federal Register
Vol. 47, No. 101
Tuesday, May 25, 1982

This section of the FEDERAL REGISTER contains documents other than rules or proposed rules that are applicable to the public. Notices of hearings and investigations, committee meetings, agency decisions and rulings, delegations of authority, filing of petitions and applications and agency statements of organization and functions are examples of documents appearing in this section.

## ADVISORY COUNCIL ON HISTORIC PRESERVATION

### Meeting

Notice is hereby given in accordance with § 800.6(d)(3) of the regulations of the Advisory Council on Historic Preservation, "Protection of Historic and Cultural Properties" (36 CFR Part 800), that a panel of five members of the Council will meet on June 21 and 22, 1982, to consider the proposal by the city of Memphis, Tennessee, to demolish the Memphis Street Railway Office and Streetcar Complex, a property determined to be eligible for inclusion in the National Register of Historic Places. The city proposes to use Community Development Block Grant Funds administered by the Department of Housing and Urban Development to carry out this activity.

Pursuant to § 800.6(b)(2) of the Council's regulations, the Chairman of the Council decided that a panel should consider this proposal in accordance with Section 106 of the National Historic Preservation Act of 1966 (16 U.S.C. 470f, as amended).

The Council was established by the National Historic Preservation Act to advise the President and Congress on matters relating to historic preservation and to comment upon Federal, federally assisted, and federally licensed undertakings having an effect upon properties listed in or eligible for inclusion in the National Register of Historic Places. The Council's members are the Secretary of the Interior, the Architect of the Capitol, the Secretary of Agriculture, and the heads of four other Federal agencies appointed by the President, one Governor and one mayor appointed by the President, the President of the National Conference of State Historic Preservation Officers, the Chairman of the National Trust for Historic Preservation, and seven private citizens appointed by the President.

The Council's regulations require that the panel be composed of five members, three from the private sector (with one chairing) and two Federal members. This panel will be chaired by Mr. Alexandria Aldrich of Saratoga Springs, New York. The panel will meet in the City Council Chamber in Memphis. The exact time has yet to be set and may be obtained from the Executive Director.

The panel will consider the written and oral statements from concerned parties. Written statements should be submitted to the Executive Director of the Council by June 1910, 1982. Persons wishing to make oral statement should notify the Exective Director by June 10, 1982. Additional information concerning the meeting of the submission of statements is available from the Executive Director, Advisory Council on Historic Preservation, Suite 530, 1522 K Street NW, Washington, DC 20005 (202-254-3495), Attn: Don L. Klima.

Dated: May 19, 1982.

**Robert R. Garvey, Jr.,**

*Executive Director.*

[FR Doc. 82-14154 Filed 5-24-82; 8:45 am]
BILLING CODE 4310-10-M

## DEPARTMENT OF AGRICULTURE

### Agricultural Stabilization and Conservation Service

### Proposed Determinations With Regard to the 1983 Wheat Program

**AGENCY:** Agricultural Stabilization and Conservation Service (ASCA), USDA.

**ACTION:** Proposed determinations.

**SUMMARY:** The Secretary of Agriculture proposes to make the following determinations with respect to the 1983 crop of wheat: (a) The loan and purchase level; (b) the established (target) price; (c) the national program acreage (NPA); (d) whether a voluntary reduction percentage should be proclaimed and, if so, the amount of such percentage reduction; (e) whether an Acreage Reduction Program (ARP) should be established and, if so, the percentage of such reduction and the method to be used in establishing the acreage bases; (f) whether a set-aside program should be established and, if so, the percentage of such set-aside; (g) whether to permit haying and grazing of conservation use acreage if an acreage reduction or set-aside program is established; (h) whether a land diversion program should be established and, if so, the extent of such diversion and the level of payment; (i) provisions of the farmer-owned reserve (FOR); (j) whether to require offsetting compliance if an Acreage Reduction Program is established; and (k) other provisions. These determinations are made in accordance with the provisions of the Agricultural Act of 1949, as amended (hereinafter referred to as the "1949 Act".

**DATE:** Comments must be received on or before June 24, 1982, in order to be assured of consideration.

**ADDRESS:** Dr. Howard C. Williams, Director, Analysis Division, USDA-ASCS, Room 3741, South Building, P.O. Box 2415, Washington, D.C. 20013.

**FOR FURTHER INFORMATION CONTACT:** Bruce R. Weber, Agricultural Marketing Specialist, Analysis Division, USDA-ASCS, P.O. Box 2415, Washington, D.C. 20013 or call (202) 447-4146. The Draft Impact Analysis describing the options considered in developing this proposed determination and the impact of implementing each option is available on request from the above-named individual.

**SUPPLEMENTARY INFORMATION:** This notice has been reviewed under USDA procedures established in accordance with Executive Order 12291 and Secretary's Memorandum No. 1512-1 and has been designated as "major". It has been determined that these program provisions will result in an annual effect on the economy of $100 million or more.

The title and number of the federal assistance programs that this notice applies to are: Title—Wheat Production Stabilization: Number 10.058 and Title—Commodity Loans and Purchases: Number 10.051, as found in the catalog of Federal Domestic Assistance.

These actions will not have a significant impact specifically on area and community development. Therefore, a review as established by OMB Circular A-95 was not used to assure that units of local Government are informed of this action.

It has been determined that the Regulatory Flexibility Act is not applicable to this Notice since ASCS is not required by 5 U.S.C. 553 or any other provision of law to publish a notice of

proposed rulemaking with respect to the subject matter of this notice.

Certain determinations set forth in this notice are required to be made by the Secretary for 1983-crop program purposes by August 15, 1982. In addition, it is necessary that the determinations for the 1983 crop be made in sufficient time to permit wheat producers to make adequate plans for the production of their crop. Therefore, I have determined that the public comment period is being limited to 30 days which will allow the Secretary sufficient time to properly consider the comments received before the final program determinations are made.

The following proposed program determinations with respect to the 1983-crop of wheat are to be made by the Secretary:

**Proposed Determinations**

a. *The Loan and Purchase Level for the 1983 Crop of Wheat.* Section 107B(a) of the 1949 Act provides that the Secretary shall make available to producers loans and purchases for the 1983 crop of wheat at such level, not less than $3.55 per bushel, as the Secretary determines wil maintain the competitive relationship of wheat to other grains in domestic and export markets after taking into consideration the cost of producing wheat, supply and demand conditions, and world prices for wheat. If the Secretary determines that the average price of wheat received by producers in any marketing year is not more than 105 percent of the level of loans and purchases for wheat for the marketing year, the Secretary may reduce the levels of loans and purchases for the next marketing year by the amount the Secretary determines necessary to maintain domestic and export markets for grain, except that the level of loans and purchases shall not be reduced by more than 10 percent in any year nor below $3.00 per bushel. Loan and purchase levels being considered for the 1983 crop of wheat range from $3.55 per bushel to $3.80 per bushel.

Comments on the level of loans and purchase rate for the 1983 crop of wheat, along with supporting data, are requested from interested persons.

b. *The Established (Target) Price Level for the 1983 Crop of Wheat.* Section 107B(b)(1)(C) of the 1949 Act provides that the established price for wheat shall not be less than $4.30 per bushel for the 1983 crop. Any such established price may be adjusted by the Secretary as the Secretary determines to be appropriate to reflect any change in (i) the average adjusted cost of production per acre for the two crop years immediately preceding the year for which the determination is made from (ii) the average adjusted cost of production per acre for the two crop years immediately preceding the year previous to the one for which the determination is made. The adjusted cost of production for each of such years may be determined by the Secretary on the basis of such information as the Secretary finds necessary and appropriate for the purpose and may include variable costs, machinery ownership costs, and general farm overhead costs, allocated to the crops involved on the basis of the proportion of the value of the total production derived from each crop.

Comments are requested from interested persons as to the amount of the established (target) price for the 1983 crop of wheat along with supporting data.

c. *The National Program Acreage (NPA).* Section 107B(c)(1) of the 1949 Act requires the Secretary to proclaim an NPA for the 1983 crop of wheat not later than August 15, 1982. The NPA shall be the number of harvested acres of wheat the Secretary determines (on the basis of the weighted national average of the farm program payment yields for the 1983 crop) will produce the quantity (less imports) that the Secretary estimates will be utilized domestically and for exports during the 1983/84 marketing year. If the Secretary determines that carryover stocks of wheat are excessive or an increase in stocks is needed to assure desirable carryover, the Secretary may adjust the NPA by the amount the Secretary determines will accomplish the desired increase or decrease in carryover stocks. The Secretary may later revise the NPA first proclaimed if the Secretary determines it is necessary based upon the latest information. If an acreage reduction program is implemented for the 1983 crop of wheat, the NPA shall not be applicable to such crop.

The U.S. wheat stock objective, an amount judged to be our "fair" share of world wheat stocks, has been determined to be equal to approximately 6.0 percent of the world consumption of wheat (this represents the approximate 10-year average of the ratio of U.S. stocks to world consumption) or approximately 992 million bushels for the 1982/83 marketing year.

If required, the likely NPA for the 1983 crop of wheat would be:

a. Estimated Domestic Use, 1983/84—865 mil. bu.
b. Plus Estimated Exports, 1983/84—1,735 mil. bu.
c. Minus Imports——2 mil. bu.
d. Minus Stock Adjustment [1]——267 mil. bu.
e. Divided by National Weighted Average Farm Program Payment Yield—34.0 bu/ac.
f. Equals 1983-Crop NPA—68.6 mil. ac.

[1] a. Estimated 1983/84 Beginning Stocks—1,289 mil. bu.
b. Minus 6.2 percent of 1982/83 World Consumption of Wheat—1,022 mil. bu.
c. Equals Desired Stock Adjustment——267 mil. bu.

No NPA was announced for the 1982 crop of wheat because the NPA provisions do not apply when an acreage reduction program is in effect. Comments on the NPA and the appropriate stocks level for the 1983 crop of wheat from interested persons, along with appropriate supporting data, are requested.

d. *Whether a Voluntary Reduction Percentage should be proclaimed and, if so, the level of such voluntary reduction percentage.* Under section 107B(c)(3) of the 1949 Act, the 1983 individual farm program acreage of wheat eligible for payments shall not be reduced by application of an allocation factor (not less than 80 percent nor more than 100 percent) if the producer reduces the acreage of wheat planted for harvest on the farm from the 1983-crop established wheat acreage base by at least the percentage recommended by the Secretary in his proclamation of the NPA for the 1983 crop. If an acreage reduction program is implemented for the 1983 crop of wheat, the voluntary reduction percentage shall not be applicable to such crop.

If required, the likely national recommended reduction percentage for the 1983-crop of wheat would be:

a. 1983 Established Wheat Acreage Base—89.1 mil. ac.
b. Minus 1983 Preliminary NPA—68.6 mil. ac.
c. Equals Acrage Acreage Reduction Needed from Acreage Base—20.5 mil. ac.
d. Divided by 1983 Wheat Acreage Base—89.1 mil. ac.
e. Equals 1983-Crop Recommended Reduction Percentage—23 percent.

Comments from interested persons with respect to the reduction percentage, if any, are requested.

e. *Whether an Acreage Reduction Program (ARP) should be established and, if so, the Percentage of such reduction and the method of establishing Acreage Bases.* Under sections 107B(e) (1) and (2) of the 1949 Act, the Secretary may establish an acreage reduction program for the 1983 crop of wheat if the Secretary determines that the total supply of wheat, in the absence of such a program, will be excessive, taking into account the need for an adequate carryover to maintain reasonable and stable supplies

and prices and to meet a national emergency. The Secretary shall announce any such wheat acreage reduction program not later than August 15 prior to the calendar year in which the crop is harvested. Such limitation shall be achieved by applying a uniform percentage reduction to the acreage base for each wheat-producing farm. Producers who knowingly produce wheat in excess of the permitted wheat acreage for the farm shall be ineligible for wheat loans, purchases; and payments with respect to that farm. The acreage base for any farm for the purpose of determining any reduction required to be made for any year as the result of a limitation shall be the acreage planted on the form to wheat for harvest in the crop year immediately preceding the year for which the determination is made or, at the discretion of the Secretary, the average acreage planted to wheat for harvest in the two crop years immediately preceding the year for which the determination is made. The Secretary may make adjustments to reflect established crop-rotation practices and to reflect such other factors as he determines should be considered in determining a fair and equitable base. In addition, a number of acres on the farm determined by dividing (1) the product obtained by multiplying the number of acres required to be withdrawn from the production of wheat times the number of acres actually planted to wheat by (2) the number of acres authorized to be planted to wheat under a limitation established by the Secretary shall be devoted to conservation uses, in accordance with regulations issued by the Secretary.

The need for an acreage reduction program for wheat in 1983 will depend on the outcome of the 1982 crop of wheat. It is estimated that the 1982-crop plantings of wheat are 87.0 million acres and the 78.5 million acres of such crop will be harvested. Total production is projected to be 2,715 million bushels, down approximately 3 percent from the record 1981 wheat crop.

It is estimated that domestic use of wheat for 1982/83 will decrease from 1981/82 (867 million bushels) to about 845 million bushels. The decrease in the domestic use of wheat will be attributable to the decline in the use of wheat for feed since the wheat/feed grain ratio will favor feed grains even more than for the 1981-crops. Domestic food use of wheat is projected to increase by a small amount and will offset some of the expected decrease in the use of wheat as feed.

Total world trade is expected to remain at approximately the same level as in the preceding year, but U.S. exports for the 1982/83 marketing year are expected to decrease to about 1700 million bushels from the estimated record of 1800 million bushels in the 1981/82 marketing year. U.S. exports for 1982/83 may vary considerably depending on world wheat production as well as the 1982-crop wheat outturn in the Soviet Union, China, and India.

Given the 1982/83 outlook, ending carryover stocks of wheat may increase by about 15 percent to nearly 1.3 billion bushels. This amount is considered excessive.

Planted and harvested acreage for the 1983 crop of wheat are estimated to remain about the same as 1982 in the absence of an acreage reduction program. Given the same acreage with a trend yield of 35.0 bushels per acre, 1983 crop production of wheat would be an estimated 2,750 million bushels. With this level of production and estimated beginning stocks of nearly 1.3 billion bushels the total supply of wheat for 1983/84 is projected to be a record 4.0 billion bushels.

Domestic use in 1983/84 is projected to increase slightly. This increase will result largely because of increased use of wheat as feed. Domestic food use is also expected to increase, although only slightly.

World trade is expected to remain strong in 1983/84. U.S. exports are estimated at 1,735 million bushels, a 2 percent increase from 1982/83 but less than the record exports in 1981/82.

Therefore, total demand for the 1983/84 marketing year is projected at 2.6 billion bushels. This would result in an ending carryover level of over 1.4 billion bushels, more than 11 percent higher than the previous year. This ending carryover level exceeds the desired level of just under 1.0 billion bushels by more than 45 percent.

The above outlook suggests that an acreage reduction program will be needed for the 1983 crop of wheat. However, later crop developments throughout the world could materially change this outlook. Options under consideration at this time include: (1) No ARP; (2) a 10 percent APR; (3) a 15 percent ARP; and (4) a 20 percent ARP.

Interested persons are encouraged to comment on the need for an acreage reduction program for the 1983-crop of wheat, and the appropriate percentage. Also under consideration is the method for establishing the wheat acreage bases for those producers participating in the 1983 program. At the present time, it is contemplated that the 1983 wheat acreage base which is established for a farm will equal the 1982 wheat acreage base established for the farm if the producer participated in the 1982 ARP. In addition, the 1983 wheat acreage base established for a farm will not be reduced below the 1982 base because a producer did not plant any of the 1982 wheat acreage base established for the farm to wheat if the proper acreage reports are filed with ASCS. It is further contemplated that a 1983 wheat acreage base will be established for the farm of a producer who did not participate in the 1982 ARP based upon the average of the 1981 and 1982 crops of wheat planted to harvest on the farm. This will assure that, in determining wheat acreage bases, a producer who did not participate in the 1982 wheat program will not gain an unfair advantage over the producers who did participate.

Interested persons are requested to comment on the method for establishing acreage bases for the 1983 crop of wheat.

f. *Whether a Set-Aside Program should be established and, if so, The Percentage of such set-aside.* Under sections 107B(e)(1) and (3) of the 1949 Act, the Secretary may establish a Set-Aside Program for the 1983 crop of wheat if the Secretary determines that the total supply of wheat, in the absence of such a program, will be excessive, taking into account the need for an adequate carryover to maintain reasonable and stable supplies and prices and to meet a national emergency. The Secretary shall announce any such wheat set-aside program not later than August 15 prior to the calendar year in which the crop is harvested. If a set-aside program is announced, then as a condition of eligibility for loans, purchases, and payments, the producers on a farm must set-aside and devote to conservation uses an acreage of cropland equal to a specified percentage, as determined by the Secretary, of the acreage of wheat plant for harvest of the crop for which the set-aside is in effect. The set-aside acreage shall be devoted to conservation uses in accordance with regulations issued by the Secretary. If a set-aside program is established, the Secretary may limit the acreage planted to wheat. Such limitation shall be applied on a uniform basis to all wheat-producing farms. The Secretary may make such adjustments in individual set-aside acreages as the Secretary determines to be necessary to correct for abnormal factors affecting production, and to give due consideration to tillable acreage, crop-rotation practices, types of soil, soil and

water conservation measures, topography, and such other factors as the Secretary deems necessary.

Interested persons are encouraged to comment on the need for a 1983 wheat set-aside program and, if so, the appropriate percentage of acreage to be set-aside.

g. *Whether to Allow Haying and Grazing of Conservation Use Acreage if an Acreage Reduction Program or Set-Aside Program is established.* Section 107B(e)(4) of the 1949 Act provides that the regulations issued by the Secretary with respect to acreage required to be devoted to conservation uses shall assure protection of such acrege from weeds and wind and water erosion.

With respect to the 1982-corp Wheat Acreage Reduction Program, producers who had planted acreage to wheat before the announcement of the provisions of the 1982 wheat program on January 29, 1982, were permitted to cut such wheat acreage for hay or to graze off such wheat acreage. While producers who did no plant wheat before January 29, 1982, were permitted to graze the conservation use acreage except during the six principal growing months, such producers were not permitted to harvest their wheat acreage for hay. In addition, specific cover corps and practices were developed at the local county ASC committee level and approved by the State ASC Committee and the State Conservationist for the 1982 conservation use acreage.

If an acreage reduction or set-aside program is announced for the 1983 crop, proposals to coordinate conservation concerns with a production adjustment program include the following: (1) Expanding the definition of land which is eligible to satisfy ARP conservation use or set-aside requirements; (2) allowing 1982 conservation use acreage to be included in the cropland base for subsequent programs; (3) giving priority for cost-sharing for conservation programs for practices installed on conservation use or set-aside acreage; and (4) permitting haying and grazing within approved guidelines on conservation use or set-aside acreage.

Interested persons are invited to comment on the grazing and haying of conservation use acreage and the conservation measures applied to land removed from production under the 1982 Acreage Reduction Programs. Also, comments are requested on what changes may be necessary to provide a greater degree of compatibility and coordination between the conservation and Acreage Reduction or Set-Aside Programs.

h. *Whether a Land Diversion Program should be established and, if so, the Extent of Such Diversion and the Level of Payments.* Section 107B(e)(5) of the 1949 Act provides that the Secretary may make land diversion payments to producers of wheat, whether or not an acreage reduction or set-aside program for wheat is in effect, if the Secretary determines that such land diversion payments are necessary to assist in adjusting the total national acreage of wheat to desirable goals. The amount payable to producers under land diversion contracts may be determined through the submission of bids for such contracts by producers in such manner as the Secretary may prescribe or through such other means as the Secretary deems appropriate. In the past, land diversion payments have been made based upon an offer rate system (i.e. specific rate per bushel times a farm program payment yield).

If land diversion payments are determined to be necessary for the 1983 crop of wheat, such payments will likely be based upon an offer rate system.

Diversion payment options under consideration include: (1) A 10 percent voluntary diversion with a 5 percent ARP; (2) a 10 percent voluntary diversion with a 10 percent ARP; (3) a 15 percent voluntary diversion with a 5 percent ARP; (4) a 5 percent voluntary diversion with a 10 percent ARP; (5) a 5 percent voluntary diversion with a 15 percent ARP; and (6) a 10 percent voluntary diversion with a 15 percent ARP. The range of options under consideration for the diversion payment rates are: (1) Equal to the actual deficiency payment rate; and (2) a flat rate per bushel ranging from $1.75 to $4.50, depending on the diversion percentage.

Interested persons are encouraged to address the need for a land diversion program, either in lieu of, or in conjunction with, an acreage reduction or set-aside program, and the appropriate terms and conditions of land diversion program.

i. *Provisions of the Farmer-Owned Reserve (FOR).* Section 110 of the 1949 Act provides that the Secretary shall formulate and administer a program under which producers of wheat will be able to store wheat when in abundant supply and extend the time for its orderly marketing. The Secretary shall provide for original or extended price support loans at such level of support as the Secretary determines appropriate, except that the loan rate shall not be less than the current level of support provided for under the wheat program established in accordance with Section 107B of the 1949 Act. The program may provide for (1) repayment of such loans in not less than three years nor more than five years; (2) payments to producers for storage in such amounts and under such conditions as are determined to be appropriate to encourage producers to participate in the program; (3) a rate of interest not less than the rate of interest charged the Commodity Credit Corporation by the United States Treasury, except that the Secretary may waive or adjust such interest as the Secretary deems appropriate; (4) recovery of amounts paid for storage, and for the payment of additional interest or other charges if such loans are repaid by producers before the market price for wheat has reached the trigger release level; and (5) conditions designed to induce producers to redeem and market the wheat securing such loans without regard to the maturity dates thereof whenever the Secretary determines that the market price for the commodity has attained a specified level (trigger release level), as determined by the Secretary. The Secretary shall announce the terms and conditions of the producer storage program as far in advance of making loans as practicable. In such announcement, the Secretary shall specify the quantity of wheat to be stored under the program which the Secretary determines appropriate to promote the orderly marketing of wheat. The Secretary may place an upper limit on the amount of wheat placed in the reserve but such upper limit may not be less than seven hundred million bushels of wheat.

The following options are under consideration for the FOR for the 1982-crop of wheat: (a) Extended loan rate for reserve entry—maintaining the loan rate at the same level as that established for 1982-crop wheat entering the reserve ($4.00) or increasing the regular loan rate which is to be established for the 1983 crop by 45 cents in order to maintain the same relationship between the extended loan rate and the regular loan rate as existed for the 1982 crop; (b) storage payments rate—maintaining the payment rate for storage at 26.5 cents per bushel or adjusting such rate to a level which will ensure adequate participation in the FOR with respect to the 1983 crop of wheat; (c) interest rate—for the first year, charging producers entering wheat in the FOR the prevailing rate of interest charged Commodity Credit Corporation for its borrowings by the United States Treasury and waiving interest for the second and third years; (d) release (trigger) level—maintaining the release (trigger) level at the 1982 level of $4.65 per bushel or increasing the release (trigger) level to reflect the costs of

production and other factors; (e) entry of wheat into the FOR—authorizing producers to enter wheat into the FOR at harvest or delaying entry into the FOR until maturity of the regular loan; and (f) quantity limit—placing no upper limit on the quantity of wheat entering the reserve program or placing an upper limit on the quantity of wheat entering the reserve program at an appropriate level above 700 million bushels.

Interested persons are encouraged to comment on these or other options dealing with the provisions of the farmer-owned wheat reserve program for the 1983 crop of wheat.

j. *Whether to require offsetting compliance if an Acreage Reduction or Set-Aside Program is established.* Under Section 107B of the 1949 Act, the Secretary may implement offsetting compliance requirements as a condition of eligibility for program benefits. If offsetting compliance is required, operators and owners of farms would have to ensure that all of their farms were either complying with program requirements such as planting within the established wheat acreage bases or the normal crop acreage established for these farms in order to be eligible for program benefits. Offsetting compliance was not in effect for the 1982 crop.

Interested persons are encouraged to comment on the need for the Secretary to require offsetting compliance for the 1983-crop of wheat if an acreage reduction program is established.

k. *Other Related Provisions.* A number of other determinations must be made in carrying out the wheat loan and purchase programs such as: (a) Commodity eligibility; (b) premiums and discounts for grades, classes, and other qualities; (c) establishment of county loan and purchase rates; and (d) such other provisions as may be necessary to carry out the programs.

Consideration will be given to any data, views and recommendations that may be received relating to the above items.

Signed at Washington, D.C., on May 21, 1982.

**Everett Rank,**

*Administrator, ASCS.*

[FR Doc. 82-14237 Filed 5-24-82; 8:45 am]

BILLING CODE 3410-05-M

## Forest Service

### Big Valley Federal Sustained Yield Unit; Public Advisory Hearing

The Modoc National Forest will sponsor a public advisory hearing on Thursday, June 24, 1982 at the Adin Community Hall in Adin, California. The purpose of the public advisory hearing is to consider the advantages and/or disadvantages of continuing for the next five year period with the present policy statement for the Big Valley Federal Sustained Yield Unit.

The public is invited to attend the hearing to obtain further information and/or to participate by giving advisory testimony. Written comments will be accepted from date of hearing through August 9, 1982.

Dated: May 17, 1982.

**C. A. Goughnour,**

*Acting Forest Supervisor.*

[FR Doc. 82-14190 Filed 5-24-82; 8:45 am]

BILLING CODE 3410-11-M

## Soil Conservation Service

### Bayou Pierre Watershed, Mississippi

**AGENCY:** Soil Conservation Service, USDA.

**ACTION:** Notice of intent to prepare an environmental impact statement.

**SUMMARY:** Pursuant to Section 102(2)(C) of the National Environmental Policy Act of 1969; the Council on Environmental Quality Guidelines (40 CFR Part 1500); and the Soil Conservation Service Guidelines (7 CFR Part 650); the Soil Conservation Service, U.S. Department of Agriculture, gives notice that an environmental impact statement is being prepared for the Bayou Pierre Watershed, Copiah and Lincoln Counties, Mississippi.

**FOR FURTHER INFORMATION CONTACT:** Billy C. Griffin, State Conservationist, Soil Conservation Service, Federal Building, 100 W. Capitol Street, Jackson, Mississippi 39269, telephone 601-960-5205.

**SUPPLEMENTARY INFORMATION:** The environmental assessment of this federally assisted action indicates that the project may cause significant local, regional, or national impacts on the environment. As a result of these findings, Billy C. Griffin, State Conservationist, has determined that the preparation and review of an environmental impact statement are needed for this project.

The project concerns a plan for watershed protection, flood prevention, and recreation. Alternatives under consideration to reach these objectives include systems for conservation land treatment, nonstructural measures, earth dams, and recreation development.

A draft environmental impact statement will be prepared and circulated for review by agencies and the public. The Soil Conservation Service invites participation and consultation of agencies and individuals that have special expertise, legal jurisdiction, or interest in the preparation of the draft environmental impact statement. Further information on the proposed action may be obtained from Billy C. Griffin, State Conservationist, at the above address.

(Catalog of Federal Domestic Assistance Program No. 10.904, Watershed Protection and Flood Prevention Program. Office of Management and Budget Circular A-95 regarding State and local clearinghouse review of Federal and federally assisted programs and projects is applicable)

Dated: May 12, 1982.

**Billy C. Griffin,**

*State Conservationist.*

[FR Doc. 82-14206 Filed 5-24-82; 8:45 am]

BILLING CODE 3410-16-M

## CIVIL AERONAUTICS BOARD

### Air Cargo, Inc.; Agreement Show Cause Proceeding

**AGENCY:** Civil Aeronautics Board.

**ACTION:** *Final Order in 82-5-106 in the Air Cargo, Inc. Agreement Show Cause Proceeding,* Docket 36592.

**SUMMARY:** The Board is issuing a final order in the Air Cargo, Inc. Agreement Show Cause Proceeding, Docket 36592, proposing to continue its approval of Agreement CAB No. 1041, as amended, to withdraw antitrust immunity, and to grant a motion of Air Freight Haulage Co., Inc., for leave to file a late reply. Agreement CAB No. 1041, as amended, was approved by the Board in Order No. E-1086, on December 31, 1947. The agreement established a carrier owned corporation, Air Cargo, Inc. (ACI) to provide either directly, through the use of its own vehicles and employees, or by contract, pick-up and delivery services, and other services desired by the airlines in connection with the transportation of air cargo. The original purpose of this agreement was to facilitate and coordinate the interline movement of air cargo over the lines of member carriers. ACI's services are available throughout the United States and Puerto Rico, to all certificated airlines, commuter airlines, cargo carriers authorized under section 418 of the Federal Aviation Act, as amended, shippers' associations, and air freight forwarders. ACI also maintains consolidated air freight terminals for certain member carriers which desire such services at two international airports, Dulles Airport (Washington, D.C.), and Ontario (Los Angeles) Airport. (The complete text of this order is available as noted below).

**DATES:** Petitions for Recommendation of this order shall be filed no later than June 14, 1982.

**ADDRESSES:** Documents should be filed in Docket 36592, Docket Section, Room 714, Civil Aeronautics Board, Washington, D.C. 20428.

**FOR FURTHER INFORMATION CONTACT:** Susan L. Blankenheimer, Competition Maintenance Division, Bureau of Domestic Aviation, Civil Aeronautics Board, 1825 Connecticut Avenue, N.W., Washington, D.C. 20428, (202) 673-5325.

**SUPPLEMENTARY INFORMATION:** A complete text of Order 82-5-106 is available from our Distribution Section, Room 100, 1825 Connecticut Avenue, N.W., Washington, D.C. Persons outside the metropolitan area may send a postcard request for Order 82-5-106 to the Distribution Section, Civil Aeronautics Board, Washington, D.C. 20428.

By the Civil Aeronautics Board: May 20, 1982.

**Phyllis T. Kaylor,**

*Secretary.*

[FR Doc. 82-14225 Filed 5-24-82; 8:45 am]

**BILLING CODE 6320-01-M**

## Application of North American Airlines, Inc. for a Charter Certificate

**AGENCY:** Civil Aeronautics Board.

**ACTION:** Notice of Order Instituting a Fitness Investigation of North American Airlines, Inc. in Docket 40511 (Order 82-5-103).

**SUMMARY:** The Board is instituting an investigation to determine the fitness of North American Airlines, Inc. to engage in the interstate and overseas charter air transportation of persons, property and mail.

**DATES:** Persons wishing to file petitions for leave to intervene in the *North American Airlines, Inc. Fitness Investigation* shall file their petitions in Docket 40511 by June 4, 1982 and shall serve such filings on all persons listed below.

**ADDRESSES:** Petitions for leave to intervene should be filed in Docket 40511 and should be addressed to the Docket Section, Civil Aeronautics Board, Washington, D.C. 20428.

In addition, copies of such filings should be served on North American Airlines; the mayor and airport manager of Omaha, Nebraska; and the Nebraska Department of Aeronautics; and on any other persons filing petitions.

**FOR FURTHER INFORMATION CONTACT:** Anne W. Stockvis, Bureau of Domestic Aviation, Civil Aeronautics Board, 1825 Connecticut Avenue, N.W., Washington, D.C. 20428, (202) 673-5198.

**SUPPLEMENTARY INFORMATION:** The complete text of Order 82-5-103 is available from our Distribution Section, Room 100, 1825 Connecticut Avenue, N.W., Washington, D.C. 20428. Persons outside the metropolitan area may send a postcard request for Order 82-5-103 to that address.

By the Civil Aeronautics Board: May 20, 1982.

**Phyllis T. Kaylor,**

*Secretary.*

[FR Doc. 82-14226 Filed 5-24-82; 8:45 am]

**BILLING CODE 6320-01-M**

## DEPARTMENT OF COMMERCE

### International Trade Administration

## Birch 3-Ply Doorskins From Japan; Tentative Determination To Revoke in Part Antidumping Finding

**AGENCY:** U.S. Department of Commerce, International Trade Administration.

**ACTION:** Notice of Tentative Determination To Rovoke in Part Antidumping Finding.

**SUMMARY:** The Department of Commerce has tentatively determined to revoke in part the antidumping finding on birch 3-ply doorskins from Japan. The tentative determination applies to one company, Marutama Industries Co., Ltd. Marutama has had no dumping margins from April 1, 1975, through December 31, 1979.

The Interested parties are invited to comment on this tentative determination.

**EFFECTIVE DATE:** May 25, 1982.

**FOR FURTHER INFORMATION CONTACT:** Brain Kelly or David R. Chapman, Office of Compliance, International Trade Administration, U.S. Department of Commerce, Washington, D.C. 20230 (202-377-2923).

**SUPPLEMENTARY INFORMATION:**

### Background

On February 16, 1976, a dumping finding with respect to birch 3-ply doorskins was published in the **Federal Register** as Treasury Decision 76-48 (41 FR 7389). The Department of Commerce ("the Department") has published the final results of its first review of the finding (46 FR 33574-5, 47 FR 1162), and, more recently, the preliminary results of its second review (47 FR 11737).

### Scope of the Determination

Imports covered by this determination are shipments of birch 3-ply doorskins manufactured by Marutama Industries Co., Ltd. ("Marutama"). Birch 3-ply doorskins are currently classifiable under items 240.1420, 240.1440, and 240.1460 of the Tariff Schedules of the United States Annotated (TSUSA). The determination applies to such doorskins sold by Marutama for export to the United States.

### Basis of Determination

Section 353.54 of the Commerce Regulations requires that for a company to apply for revocation, two conditions must usually be met: (1) sales at not less than fair value for at least a two year period following publication of a finding or order, and (2) an agreement by the parties subject to the revocation to reinstatement of the finding or order in the case of subsequent less than fair value sales. During the period April 1, 1975, through December 31, 1979, Marutama made all sales at not less than fair value.

In addition, Marutama has agreed in writing to an immediate suspension of liquidation and reinstatement of the finding if circumstances develop that indicate that the merchandise thereafter manufactured and sold by Marutama for export to the United States is being sold at less than fair value. As a result, we tentatively determine to revoke the antidumping finding on birch 3-ply doorskins with respect to Marutama Industries Co., Ltd. Such revocation, if made final, shall apply to all unliquidated entries of the merchandise entered, or withdrawn from warehouse, for consumption on or after the date of publication of this notice.

Interested parties may submit written comments on this tentative determination on or before June 24, 1982 notice and may request disclosure and/or a hearing on or before June 4, 1982. Any hearing, if requested, will be held 30 days after publication of this notice or the first workday thereafter. The Department will publish the results of its analysis of any such comments or hearing.

This tentative determination to revoke in part is in accordance with section 751(c) of the Tariff Act of 1930 (19 U.S.C. 1675(c)) and § 353.54 of the Commerce Regulations (19 CFR 353.54).

**Gary N. Horlick,**

*Deputy Assistant Secretary for Import Administration.*

May 19, 1982.

[FR Doc. 82-14220 Filed 5-24-82; 8:45 am]

**BILLING CODE 3510-25-M**

## COMMITTEE FOR THE IMPLEMENTATION OF TEXTILE AGREEMENTS

### Announcement of Additional Import Controls and Adjusting Existing Levels for Certain Cotton, Wool, and Man-Made Fiber Textile Products From the Republic of the Philippines

**AGENCY:** Committee for the Implementation of Textile Agreements.

**ACTION:** (1) Controlling imports of wool gloves and mittens in Category 431 and women's, girls', and infants' trousers of man-made fibers in Category 648 (pt.), produced or manufactured in the Philippines and exported in the United States during the twelve-month period which began on January 1, 1982, at respective levels of 53,971 dozen pairs and 54,336 dozen. The level for Category 431 has been adjusted to account for 1981 overshipments amounting to 2,445 dozen.

(2) Reducing the level of restraint for women's, girls', and infants' woven cotton blouses in Category 341 (pt.) by 19,970 dozen, representing 1981 overshipments through March 31, 1982, to 46,732 dozen.

(A detailed description of the textile categories in terms of T.S.U.S.A. number was published in the **Federal Register** on February 28, 1980 (45 FR 13172), as amended on April 23, 1980 (45 FR 27463), August 12, 1980 (45 FR 53506), December 24, 1980 (45 FR 85142), May 5, 1981 (46 FR 25121), October 5, 1981 (46 FR 48963), October 27, 1981 (46 FR 52409), February 9, 1982 (47 FR 5926) and May 13, 1982 (47 FR 20654)).

**SUMMARY:** Under the terms of the Bilateral Cotton, Wool, and Man-Made Fiber Textile Agreement of August 22 and 24, 1978, as amended, between the Governments of the United States and the Republic of the Philippines, the United States Government has decided to control imports of cotton, wool, and man-made fiber textile products in Categories 431 and 648 (pt.), produced or manufactured in the Philippines and exported to the United States during the twelve-month period which began on January 1, 1982, in addition to those categories previously designated. Overshipments from 1981 are also being charged to Categories 431 and 341 (pt.).

**EFFECTIVE DATE:** May 26, 1982.

**FOR FURTHER INFORMATION CONTACT:** Carl Ruths, International Trade Specialist, Office of Textiles and Apparel, U.S. Department of Commerce, Washington, D.C. 20230 (202/377-4212).

**SUPPLEMENTARY INFORMATION:** On December 18, 1981, there was published in the **Federal Register** (46 FR 61688) a letter dated December 14, 1981 from the Chairman of the Committee for the Implementation of Textile Agreements to the Commissioner of Customs, which established levels of restraint for certain specified categories of cotton, wool, and man-made fiber textile products, including Category 341 (pt.), produced or manufactured in the Philippines, which may be entered into the United States for consumption, or withdrawn from warehouse for consumption, during the twelve-month period which began on January 1, 1982 and extends through December 31, 1982. Under the terms of the bilateral agreement, the United States Government has decided also to control imports of wool and man-made fiber textile products in Categories 431 and 648 (pt.) during the same period and to adjust the levels for Categories 341 pt. and 431 to account for 1981 overshipments. Accordingly, in the letter published below the Chairman of the Committee for the Implementation of Textile Agreements directs the Commissioner of Customs to prohibit entry for consumption, or withdrawal from warehouse for consumption, of coton, wool, and man-made fiber textile products in Category 341 (pt.), 431, and 648 (pt.) in excess of the designated, adjusted levels of restraint. The newly-established levels for Categories 431 and 648 (pt.) have not been adjusted to account for any imports after December 31, 1981. Imports in Category 431 have amounted to 845 dozen pairs and 7,500 dozen in Category 648 (pt.) through March 31, 1982 and will be charged. As the data become available, further charges will be made to account for imports during the period which began on April 1, 1982 and extends to the effective date of this action.

**Paul T. O'Day,**

*Chairman, Committee for the Implementation of Textile Agreements.*

May 20, 1982.

**Committee for the Implementation of Textile Agreements**

Commissioner of Customs
*Department of the Treasury, Washington, D.C. 20229*

Dear Mr. Commissioner: This directive amends, but does not cancel, the directive of December 14, 1981 from the Chairman, Committee for the Implementation of Textile Agreements, concerning imports into the United States of certain cotton, wool and man-made fiber textile products, produced or manufactured in the Philippines.

Effective on May 26, 1982, paragraph 1 of the directive of December 14, 1981 is amended to include an adjusted level of restraint for cotton textile products in Category 341 (pt.)[1] of 46,732 dozen.[2]

Also effective on May 26, 1982, paragraph 1 of the directive of December 18, 1981 is further amended to include the following levels of restraint for wool and man-made fiber textile products in Categories 431 and 648 (pt.)

| Category | 12-mo. level of restraint[1] |
|---|---|
| 431 | 53,971 dozen pairs. |
| 648 pt.[2] | 54,336 dozen. |

[1] The levels of restraint have not been adjusted to reflect any imports after December 31, 1981. Imports through March 31, 1982 have amounted to 845 dozen pairs in Category 431 and 7,500 dozen in Category 648 (pt.).

[2] In Category 648, all T.S.U.S.A. numbers except 383.1940, 383.8146, 383.2250, and 383.9071.

Wool and man-made fiber textile products in Categories 431 and 648 pt., which have been exported to the United States prior to January 1, 1982, shall not be subject to this directive.

Wool and man-made fiber textile products in Categories 431 and 648 pt., which have been released from the custody of the U.S. Customs Service under the provisions of 19 U.S.C. 1448(b) and 1484(a)(1)(A) prior to the effective date of this directive shall not be denied entry under this directive.

(A detailed description of the textile categories in terms of T.S.U.S.A. numbers was published in the **Federal Register** on February 28, 1980 (45 FR 13172), as amended on April 23, 1980 (45 FR 27463), August 12, 1980 (45 FR 53506), December 24, 1980 (45 FR 85142), May 5, 1981 (46 FR 25121), October 5, 1981 (46 FR 489630, October 27, 1981 (46 FR 52409), February 9, 1982 (47 FR 5926) and May 13, 1982 (47 FR 20654)

In carrying out the above directions, the Commissioner of Customs should construe entry into the United States for consumption to include entry for consumption into the Commonwealth of Puerto Rico.

The actions taken with respect to the Government of the Republic of the Philippines and with respect to imports of cotton, wool, and man-made fiber textile products from the Philippines have been determined by the Committee for the Implementation of Textile Agreements to involve foreign affairs functions of the United States. Therefore, these directions to the Commissioner of Customs, which are necessary for the implementation of such actions fall within the foreign affairs exception to the rule-making provisions of 5 U.S.C. 553. This letter will be published in the **Federal Register.**

[1] In Category 341, only T.S.U.S.A. numbers 383.0506, 383.4704, 383.4707, and 383.4711.

[2] The levels of restraint have not been adjusted to reflect any imports after December 31, 1981. Imports through March 31, 1982 have amounted to 845 dozen pairs in Category 431 and 7,500 dozen in Category 648 (pt.).

Sincerely,

Paul T. O'Day,

*Chairman, Committee for the Implementation of Textile Agreements.*

[FR Doc. 82-14219 Filed 5-24-82; 8:45 am]

BILLING CODE 3510-25-M

## DEPARTMENT OF DEFENSE

### Office of the Secretary

### Membership of the Office of the Secretary of Defense (OSD) Performance Review Board

**AGENCY:** Defense Department.

**ACTION:** Notice of Membership of the Office of the Secretary of Defense Performance Review Board.

**SUMMARY:** This notice announces the appointment of the members of the Performance Review Board (PRB) of the Office of the Secretary of Defense, OSD Field Activities, the Organization of the Joint Chiefs of Staff, the U.S. Court of Military Appeals, and the U.S. Mission to NATO. The publication of PRB membership is required by 5 U.S.C. 4314(c)(4).

The Performance Review Board provides fair and impartial review of Senior Executive Service performance appraisals and makes recommendations regarding performance and performance awards to the Secretary of Defense.

**EFFECTIVE DATE:** June 1, 1982.

**FOR FURTHER INFORMATION CONTACT:** Mrs. Sharon B. Brown, Chief, Senior Executive Service Division, Directorate for Personnel & Security, WHS, Office of the Secretary of Defense, Department of Defense, The Pentagon, (202) 695-4573 or 695-9313.

**SUPPLEMENTARY INFORMATION:** In accordance with 5 U.S.C. 4314(c)(4), the following are names and titles of the executives who have been appointed to serve as members of the Performance Review Board. They will serve a one-year renewable term, effective June 1, 1982.

M. S. Healy,

*OSD Federal Register Liaison Officer, Washington Headquarters Services, Department of Defense.*

May 19, 1982.

### Office of the Secretary of Defense Performance Review Board

*Immediate Office*

Puritano, Vincent (NMN), The Executve Assistant to the Deputy Secretary of Defense

Dolvin, Welborn G., Deputy Negotiator for the DOD for Panama Canal Treaty Affairs and Joint Chiefs of Staff

Representative, Mutual and Balanced Force Reductions Negotiations

Troia, Kathleen M., Assistant to the Secretary of Defense

Leftwich, Norma B., Director, Small and Disadvantaged Business Utilization

Crouch, Horace J., Director of Small Business and Economic Utilization Policy

Williams, Arthur F., Director, Disadvantaged Business Utilization Policy

Michel, Werner E., Inspector General for Defense Intelligence

*Office of the Under Secretary of Defense for Policy*

Lindstrom, Talbot S., Special Assistant to the Under Secretary of Defense for Policy

Turner, Robert F., Special Assistant to the Under Secretary of Defense for Policy

*Office of Net Assessment*

Marshall, Andrew W., Director of Net Assessment

*Office of the Deputy Under Secretary of Defense for Policy*

Stilwell, Richard G., Deputy Under Secretary of Defense (Policy)

Stivers, Ronald H., Assistant Deputy Under Secretary of Defense (Policy)

Alderman, Craig (NMN), Director, Emergency Planning

Reynolds, Herbert A., Deputy Director for Intelligence and Space Policy

Knapp, Harold A., Deputy Director, Joint Program Office

Snider, L. Britt, Director, Counterintelligence and Security Policy

Donnelly, John F., Director, Counterintelligence and Investigative Programs

Van Cook, Arthur F., Director, Information Security

Anderson, Maynard C., Director for Security Plans and Programs

Nielsen, Donald E., Director, Special Advisory Staff

Campen, Alan D., Director, Command and Control Policy

*Office of the Assistant Secretary of Defense (International Security Policy)*

Zakheim, Dov S., Special Assistant to the Assistant Secretary of Defense (International Security Policy)

Bryen, Stephen D., Deputy Assistant Secretary of Defense (International Economics, Trade, and Security Policy)

Lehman, Ronald F. II, Deputy Assistant Secretary of Defense (Strategic and Theater Nuclear Forces Policy)

Minichiello, Lee P., Assistant Deputy Director for Strategic Systems and Senior OSD Advisor (Salt Overseas Element)

Mobbs, Michael H., Representative of the Office of the Secretary of Defense on the Strategic Arms Reduction Talks (START) Delegation

Bader, George W., Deputy Director, European and NATO Affairs

Jefferson, Ralph H., Special Assistant to the Deputy Assistant Secretary of Defense (European and NATO Affairs)

*Office of the Assistant Secretary of Defense (International Security Affairs)*

Koch, Noel C., Principal Deputy Assistant Secretary of Defense (International Security Affairs)

Shilling, David M., Director, General Purpose Forces Policy

Barringer, Philip E., Director, Foreign Military Rights Affairs

Armitage, Richard L., Deputy Assistant Secretary of Defense (East Asia and Pacific Affairs)

Woods, James L., Director, Africa Region

Denoon, David B. H., Deputy Assistant Secretary of Defense (International Economic and Energy Affairs)

Gaffney, Henry H., Jr., Director, Security Assistance Plans

Groth, Carl H., Jr., Director, International Economic Affairs

Tyler, John T., Jr., Deputy Director, Security Assistance Plans and Programs

Sanchez, Nestor D., Deputy Assistant Secretary of Defense (Inter-American Affairs)

*Defense Security Assistance Agency*

Ligon, Walter B., Special Assistant to the Director, DSAA

Morris, Herbert K., Comptroller, DSAA

Murrell, Billy C., Deputy Comptroller, DSAA

Rudd, Glenn A., Director, Security Assistance Operations

Woods, James R., Director, Joint Financial Management Office

*Office of the Under Secretary of Defense for Research and Engineering*

Berenson, Paul J., Staff Specialist for Assessement and Executive Officer, Defense Science Board

Thomas, Ronald D., Director for Program Control and Administration

Wagner, Richard L., Jr., Assistant to the Secretary of Defense (Atomic Energy)

Tobriner, Matthew, W., Senior Analyst for Long Range Resource Planning

Michael, Louis G., Deputy Assistant to the Secretary of Defense (Atomic Energy) (Long Range Resource Planning)

Gold, Theodore S., Deputy Assistant to the Secretary of Defense (Chemical Matters)
Long, William A., Deputy Under Secretary of Defense (Acquisition Management)
Gordon, Harvey J., Assistant Deputy Under Secretary of Defense (Acquisition)
Fisher, Herbert L., Director, Contract Placement and Administration
Brannan, James T., Director, Defense Acquisition Regulatory System
Kendig, John L., Director, Cost, Pricing and Finance
Smith, John E., Director, Major Systems Acquisition
Martin, Edith M., Deputy Under Secretary of Defense (Research and Advanced Technology)
Millburn, George P., Special Assistant to Deputy Under Secretary (Research and Advanced Techonology)
Feinstein, Joseph (NMN), Director, Electronics and Physical Sciences
Musa, Samual A., Staff Specialist for Electronic Warfare and Target Acquisition
MacCallum, John M., Jr., Staff Specialist for Search and Surveillance
Dashiell, Thomas R., Staff Specialist for Chemical Technology
Siewert, Raymond F., Jr., Director (Engineering Technology)
Dix, Donald M., Staff Specialist for Vehicle Propulsion
Thorkildsen, Ray, Staff Specialist for Ordnance
Persh, Jerome, Staff Specialist for Materials and Structures
Kopcsak, George C., Staff Specialist, Weapons Technology
Young, Leo (NMN), Director for Research and Technical Information
Jones, Thomas K., Deputy Under Secretary of Defense (Strategic and Theater Nuclear Forces)
Butler, Gunning, Jr. (NMN), Director, Start and Arms Control Office
Gardner, John L., Director, Defense Systems
Winter, William H., Staff Specialist for Defensive Systems
Bertapelle, Arther H., Staff Specialist, Early Warning and Attack Assessment
Atkins, Marving C., Director (Offensive and Space Systems)
Ruffine, Richard S., Staff Specialist for Technology and Analysis (Offensive Systems)
Forsythe, Conrad O., Staff Specialist for Space and Advanced Systems
Bernard, Charles W., Director, Office of Land Warfare
Minneman, Milton J., Director, Mobility and Special Projects
Horton, Cyril F., Staff Specialist for Air Mobility
O'Neil, William D., III, Director, Naval Warfare
Delaney, Robert P., Staff Specialist for Anti-Submarine and Mine Systems
Anderson, David L., Staff Specialist for Naval Projection and Anti-Air Systems
King, Paul D., Staff Specialist for Interdiction/Naval Strike
Linder, Isham W., Director, Defense Test and Evaluation
Greenlee, Donald R., Staff Specialist for Strategic and Naval Warfare Systems
Richardson, William A., Deputy Director for Test Facilities and Resources
Watt, Charles K., Deputy Director, Strategic and Naval Warfare Systems
Lorenzo, Michael (NMN), Deputy Under Secretary of Defense (International Programs and Technology)
Lomacky, Oles (NMN), Director, Technology Trade
Mintz, Jeanne S., Special Assistant for Planning and Requirements
Kapper, Francis B., Director, Technology Export
Greinke, Everett D., Director for NATO/European Affairs
Sullivan, Gerald D., Director, Far East, Middle East and Southern Hemisphere Affairs
Latham, Donald C., Deputy Under Secretary of Defense (C3I)
Quinn, Thomas P., Assistant Deputy Under Secretary of Defense (Communications, Command and Control)
Facey, Albert G., Jr., Staff Specialist for Switched and Special Purpose Communications Systems
Thomas, Reynold (NMN), Jr., Staff Specialist for WWMCCS and Other C3 Systems Architecture
Cittadino, John C., Director, Theater and Tactical C3
Marquis, Dennis C., Special Assistant for NATO and European Theater Command and Control
Howe, Richard G., Staff Specialist, Tactical Command and Control
Porter, John M., Director, Electronic Warfare and C3 Countermeasures
Lewis, William J., Staff Specialist for Electronic Warfare and C3 Countermeasures
Walker, Stephen T., Director, Information Systems
Sullivan, Alden P., Director, C3 Resources
Hawkins, Charles A., Jr., Assistant Deputy Under Secretary of Defense (Intelligence)
Keller, Michael I., Senior Staff Specialist for Reconnaissance, Surveillance and Target Acquisition
Solomon, David L., Assistant Deputy Under Secretary of Defense (Technical Policy and Operations)
Salton, George L., Director, Communications Systems
Turner, Robert D., Assistant Deputy Under Secretary of Defense (Systems Integration)
Starr, Stuart H., Director, Systems Research and Evaluation
Mittino, John A., Assistant Deputy Under Secretary of Defense (Procurement Policy)
Stimson, Richard A., Director, Standardization and Acquisition Support
Grove, H. Mark, Director, Embedded Computer Resources
Donnelly, Richard E., Director, Production Resources
Hamilton, Dale L., Staff Specialist for Satellite Communications Systems

*Defense Advanced Research Projects Agency*

Cooper, Robert S., Director, Defense Advanced Research Projects Agency
Romney, Carl F., Deputy Director for Research
Lynn, Verne L., Deputy Director for Technology
Tether, Anthony J., Assistant Deputy Director for Technology
Charvonia, David A., Director, Darpa Regional Office, Europe
Sepucha, Robert C., Assistant Director for Space Defense Technology
Mangano, Joseph A., Assistant Director for Technology, Directed Energy Office
Tanimoto, Douglas H., Director, Directed Energy Office
Chapman, Ray E., Director, Program Management Office
Goodwyn, James C., Deputy Director, Program Management Office
Kahn, Robert E., Director, Information Processing Techniques Office
Levinthal, Elliot C., Director, Defense Sciences Office
Vanreuth, Edward C., Assistant Director, Material Sciences
Reynolds, Richard A., Deputy Director, Defense Sciences Office
Fields, Craig I., Assistant Director for Cybernetics Technology
Thomas, Carl M., Director, Strategic Technology Office
Pike, H. Alan, Deputy Director, Directed Energy Office
Tegnelia, James A., Jr., Director, Air Vehicles Technology Office
Whitman, Edward C., Assistant Director for Ocean Monitoring and Control
Cerf, Vinton G., Principal Research Manager (Information Processing Techniques Office)
Fraser, James C., Assistant Director, Surveillance
Hansen, John W., Deputy Director, Tactical Technology Office

*Office of the Assistant Secretary of Defense (Manpower, Reserve Affairs and Logistics)*

Shaw, Dennis R., Principal Director, Office of the Deputy Assistant Secretary of Defense (Reserve Affairs)
Juliana, James N., Principal Deputy Assistant Secretary of Defense (Manpower, Reserve Affairs and Logistics)
Shorey, Russell R., Director for Acquisition and Support Planning
Groover, Charles W., Deputy Assistant Secretary of Defense (Program Integration)
Donovan, Paul (NMN), Principal Director, Office of the Deputy Assistant Secretary of Defense (Program Integration)
Tahtinen, Dale R., Director, Mobilization Planning and Requirements
Culosi, Salvatore J., Director, Force Readiness and Sustainability Requirements and Analysis
Compton, James M., Director, International Logistics and Support Analysis
Sicilia, Thomas G., Director, Research and Data
Bergmann, Walter B., II, Director, Resource Management and Analysis
Calhoun, Jerry L., Deputy Assistant Secretary of Defense (Civilian Personnel Policy)
Earich, Douglas R., Director, Management Studies
Green, David H., Director, Personnel-Management
Garnett, Thomas F., Deputy Director for Labor-Management Relations
Coakley, William F., Director, Overseas and Nonappropriated Fund Personnel Management
Haughton, Claiborne D., Jr., Director for Civilian Equal Opportunity Programs
Stone, Robert A., Deputy Assistant Secretary of Defense (Program Management)
Farbrother, Douglas D., Principal Director, Office of the Deputy Assistant Secretary of Defense (Facilities, Environment, and Economic Adjustment)
Tillson, John C., Director, Manpower Management
Fites, Jeanne B., Director, Intergovernmental Affairs
Tucker, Alvin (NMN), Director for Training and Education
Webster, Richard D., Deputy Assistant Secretary of Defense (Supply, Maintenance and Transportation)
Altizer, Harrell B., Principal Director, Office of the Deputy Assistant Secretary of Defense (Logistics and Materiel Management)
Rauner, Robert M., Director, Office of Installations and Economic Adjustment
Shriber, Maurice M., Director for Supply Management Policy
McCarthy, Herbert W., Deputy Director, Supply Policy and Programs
Moore, Robert J., Deputy Director, Materiel Management Systems Division
Hyman, Paul J., Director, Transportation and Distribution Policy
Moore, Robert H., Staff Director, Transportation Systems Division
Turke, Joseph G., Director for Maintenance Policy
Smiley, Orville L., Director, Automated Systems
Lanoue, Robert J., Director, NATO Programs and Foreign Construction
Buzalski, Ernest A., Assistant Director for Installations Programs
Nelson, Wayne S., Director for Safety and Occupational Health Policy
Sharkey, William J., Jr., Director for Energy Policy
Meehan, Patrick J., Director, Facility Requirements and Resources
Lynch, John E., Economic Advisor
Lord, Sharon B., Deputy Assistant Secretary of Defense (Equal Opportunity and Safety Policy)

*Department of Defense Dependents Schools*

Killin, Edward C., Director, Pacific Region, Dodds

*Office of Economic Adjustment*

Robertson, William B., Assistant to the Director, Office of Economic Adjustment, for Business and Resource Development
Winshurst, Thomas H. E., Assistant Director for Operations

*Office of the Assistant Secretary of Defense (Legislative Affairs)*

Garcia, Ernest E., Deputy Assistant Secretary of Defense (Senate Affairs)
Barry, Albert P., Deputy Assistant Secretary of Defense (House Affairs)

*Office of the Assistant Secretary of Defense (Comptroller)*

Quetsch, John R., Principal Deputy Assistant Secretary of Defense (Comptroller)
Lose, Graydon I., Special Assistant for Appropriation Liaison
Rosen, E., Deputy Assistant Secretary of Defense (Management Systems)
Kraft, Herbert H., Jr., Principal Assistant to the Deputy Assistant Secretary of Defense (Management Systems)
Crehan, John T., Director for Accounting Policy
McCarty, Thomas F., Director for Cost Accounting Policy
Saylor, James W., Director, Financial Accounting Policy
Mulcahy, Kenneth C., Director, Policy Promulgation Division
Toulme, Clarence V., Director for Banking, International Finance and Professional Development
Carabello, John M., Director for Data Automation
Leary, William H., III, Associate Director, Data Automation
Scott, Winfield S., Director for Management Information Control and Analysis
Kammerer, Joseph T., Deputy Assistant Secretary of Defense (Cost and Audit)
Glaister, Clyde O., Deputy Assistant Secretary of Defense (Program/Budget)
Harshman, Richard A., Deputy Comptroller (Program/Budget)
Dube, Lawrence P., Director for Operations
McLaughlin, Frank I., Deputy Director for Operations
Russ, John M., Director for Program and Financial Control
Hessler, David J., Director for Research and Development
Eaton, Nelson W., Deputy Director for Research and Development
South, Allen D., Director for Construction
Beach, John W., Director for Plans and Systems
Trodden, Stephen A., Director for Procurement
Davidson, Ronald A., Deputy Director for Procurement
Conte, Albert V., Director for Military Personnel
Cooke, David O., Deputy Assistant Secretary of Defense (Administration)/Director, Washington Headquarters Services
Goldberg, Alfred (NMN), Policy Analyst and Historian
Ehlers, Arthur H., Jr., Director for Organizational and Management Planning
Cavaney, William T., Director, Defense Privacy Office/Executive Secretary, Defense Privacy Board
Schmidt, Raymond E., Deputy Comptroller for Audit Policy

*Office of the Assistant Secretary of Defense (Health Affairs)*

Beary, John F., III, Principal Deputy Assistant Secretary of Defense (Health Affairs)
Johns, John H., Deputy Assistant Secretary of Defense (Drug and Alcohol Abuse Prevention )
Wood, Theodore D., Director, Office of the Civilian Health and Medical Program of the Uniformed Services
McKenzie, Vernon (NMN), Deputy Assistant Secretary of Defense (Health Resource Management)

*Office of the Director, Program Analysis and Evaluation*

Chu, David S. C., Director, Program Analysis and Evaluation
Leonard, Michael (NMN), Deputy Director (Regional Programs)
Tapparo, Frank A., Director, Asia Division
Kugler, Richard L., Director, Europe Division
Major, Philip L., Deputy Director (Strategic Programs)
Ioffredo, Michael L., Director, Strategic Defensive and Theater Nuclear Forces Division
Margolis, Milton A., Deputy Director (Resource Analysis)
Morgan, John D., Director, Cost Analysis Division
Christie, Thomas P., Deputy Director (General Purpose Programs)
Pennington, Arthur, W., Director, Naval Forces Division
Finsterle, James C., Director, Land Forces Division
Croteau, Robert J., Director, Tactical Air Division
Christie, Deborah P., Director, Mobility Forces Division
McNichol, David L., Director, Economic Analysis Division

*Office of the Assistant Secretary of Defense (Public Affairs)*

Welles, Benjamim (NMN), Principal Deputy Assistant Secretary of Defense (Public Affairs)
Hinkle, Charles W., Director, Freedom of Information and Security Review
Cranston, Robert (NMN), Director, American Forces Information Service
Sheils, Marylou, Special Assistant to the Assistant Secretary of Defense (Public Affairs)

*Office of the General Counsel*

Niederlehner, Leonard (NMN), Deputy General Counsel
Baker, Walter A., Assistant General Counsel (International)
Trosch, Dennis H., Assistant General Counsel (Logistics)
Briskin, Manuel (NMN), Assistant General Counsel (Fiscal Matters)
Gilliat, Robert L., Assistant General Counsel (Manpower and Health Affairs)
Buck, Kathleen A., Assistant General Counsel (Legal Counsel)

*Office of the Assistant to the Secretary of Defense (Review and Oversight)*

Sherick, Joseph H., Assistant to the Secretary of Defense (Review and Oversight)
Vander Schaaf, Derek J., Principal Deputy Assistant to the Secretary of Defense (Review and Oversight)
Bruh, Brian M., Deputy Assistant to the Secretary of Defense (Criminal Investigations)/Director Criminal Investigative Service
Lieberman, Richard D., Deputy Assistant to the Secretary of defense (Follow-Up, Reports and Management)
Maldonado, Joe P., Director, Contract Audit Follow-Up
Lieberman, Robert J., Director, Audit Resolution and Internal Audit and Investigative Follow-Up
Calais, Mary J., Director, Special Projects and Analyis
Woehrle, Charles D., Deputy Assistant (Oversight, Evaluation and Criminal Policy)

*U.S. Mission to NATO*

Legere, Laurence J., Defense Advisor, U.S. Mission to NATO
Calaway, Paul R., Deputy Defense Advisor for Research, Engineering and Acquisition
Phillips, Gary R. Director, Defense Plans Division
Loveland, Trafton J., Director, Infrastructure and Logistics Division
Gontarek, Stanley J., Director, Communications and Electronics Division

*Washington Headquarters Services*

Snider, Larry E., Director, Space Management and Services
Sungenis, Joseph R., Director, Information Operations and Reports
Becker, Karl F., Director of Personnel and Security
Cratch, Geoffrey A., Director of Budget and Finance
Colson, Janet (NMN), International Affairs Advisor

*International Military Activities Staff—NATO*

Smith, Homer D., Jr., Director of Logistics (International Staff)
Spaulding, Harry S., Director of Logistics (NAMSA)
Miner, Francis (NMN), Director of Finance, Central European Operating Agency (NATO Support Group)
Martin, John D., Director, Nuclear Planning (International Staff)

*Organization of the Joint Chiefs of Staff*

Lese, William G., Jr., Scientific and Technical Advisor to the Chief, Saga and Chief, Technical Support Division

*U.S. Court of Military Appeals*

Granahan, Thomas F., Clerk of the Court

*Defense Audit Service*

Melchner, John W., Director, Defense Audit Service
Curry, James H., Deputy Director, Defense Audit Servitce

*Defense Communications Agency*

Whealen, John T., General Counsel

*Defense Contract Audit Agency*

Starrett, Charles O., Director, DCAA
Brown, James E., Deputy Director
Quill, John J., Counsel

*Defense Investigative Service*

O'Brien, Thomas J., Director, Defense Investigative Service

*Defense Logistics Agency*

Kabeiseman, Karl W., Counsel, Defense Logistics Agency

*Defense Nuclear Agency*

Conrad, Edward E., Deputy Director (Science and Technology)

[FR Doc. 82-14201 Filed 5-24-82; 8:45 am]
BILLING CODE 3810-01-M

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## Office of the Secretary of Defense

### Department of Defense Wage Committee; Closed Meetings

Pursuant to the provisions of section 10 of Pub. L. 92-463, the Federal Advisory Committee Act, notice is hereby given that a meeting of the Department of Defense Wage Committee will be held on Tuesday, July 6, 1982; Tuesday, July 13, 1982; Tuesday, July 20, 1982; and Tuesday, July 27, 1982 at 10 a.m. in Room 3D321, the Pentagon, Washington, DC.

The Committee's primary responsibility is to consider and submit recommendations to the Assistant Secretary of Defense (Manpower, Reserve Affairs, and Logistics) concerning all matters involved in the development and authorization of wage schedules for federal prevailing rate employees pursuant to Pub. L. 92-392. At this meeting, the Committee will consider wage survey specifications, wage survey data, local wage survey committee reports and recommendations, and wage schedules derived therefrom.

Under the provisions of section 10(d) of Pub. L. 92-463, meetings may be closed to the public when they are "concerned with matters listed in 5 U.S.C. 552b." Two of the matters so listed are those "related solely to the internal personnel rules and practices of an agency," (5 U.S.C. 552b. (c)(2)), and those involving "trade secrets and commercial or financial information obtained from a person and privileged or confidential" (5 U.S.C. 552b. (c)(4)).

Accordingly, the Deputy Assistant Secretary of Defense (Civilian Personnel Policy) hereby determines that all portions of the meeting will be closed to the public because the matters considered are related to the internal rules and practices of the Department of

Defense (5 U.S.C. 552b. (c)(2)), and the detailed wage data considered by the Committee during its meetings have been obtained from officials of private establishments with a guarantee that the data will be held in confidence (5 U.S.C. 552b. (c)(4)).

However, members of the public who may wish to do so are invited to submit material in writing to the chairman concerning matters believe to be deserving of the Committee's attention. Additional information concerning this meeting may be obtained by writing the Chairman, Department of Defense Wage Committee, Room 3D264, the Pentagon, Washington, D.C. 20301.

M. S. Healy,

*OSD Federal Register Liaison Officer, Department of Defense.*

May 20, 1982.

[FR Doc. 82-14223 Filed 5-24-82; 8:45 am]

BILLING CODE 3810-01-M

## DEPARTMENT OF EDUCATION

### Intergovernmental Advisory Council on Education; Meeting

**AGENCY:** Intergovernmental Advisory Council on Education.

**ACTION:** Notice of meeting.

**SUMMARY:** This notice sets forth the schedule and proposed agenda of a meeting of the Intergovernmental Advisory Council on Education. Notice of this meeting is required under Section 10(a)(2) of the Federal Advisory Committee Act.

**DATES:** June 10–11, 1982.

**ADDRESS:** Hubert H. Humphrey Building, 200 Independence Avenue SW., Room 800, Washington, D.C. 20201.

**FOR FURTHER INFORMATION CONTACT:** Laverne Johnson, Office of the Deputy Under Secretary for Intergovernmental and Interagency Affairs, Department of Education, 400 Maryland Avenue SW., Washington, D.C. 20202 (202) 472–6464.

**SUPPLEMENTARY INFORMATION:** The Intergovernmental Advisory Council on Education is established under Section 213 of the Department of Education Organization Act (20 U.S.C. 3423). The Council is established to provide assistance and make recommendations to the Secretary and the President concerning intergovernment policies and relations relating to education.

The meeting of the Council is open to the public. The meeting is scheduled for 2 p.m. to 4:30 p.m. on June 10 and will continue on June 11 from 9:00 a.m. to 4:30 p.m.

The proposed agenda includes:

—Procedural activities associated with organization of recently appointed Council.

—Identification of issues for Council attention.

Records are kept of all Council proceedings, and are available for public inspection at the office of the Intergovernmental Advisory Council on Education, 400 Maryland Avenue SW., Room 1079, Washington, D.C.

Signed at Washington, D.C. on Thursday, May 20, 1982.

**John H. Rodriguez,**

*Deputy Under Secretary for Intergovernmental and Interagency Affairs.*

[FR Doc. 82-14222 Filed 5-24-82; 8:45 am]

BILLING CODE 4000-01-M

## DEPARTMENT OF ENERGY

### Bonneville Power Administration

### Additional Public Hearings on Proposed Impact Aid Payments and Formula

**AGENCY:** Bonneville Power Administration (BPA), DOE.

**ACTION:** Notice of additional public hearings on proposed impact aid payments formula.

**SUMMARY:** On May 13, 1982, BPA published in the **Federal Register** (47 FR 20657) its "Notice of Proposed Impact Aid Payments Formula and Opportunities for Public Review and Comment." In addition to the five public hearings cited in this previous **Federal Register** notice, BPA has scheduled three additional public hearings.

**DATES:** The additional dates and locations are: Tuesday, May 25, 1982, Thompson Falls Elementary School, Columbia and Haley Streets, Thompson Falls, Montana; Wednesday, May 26, 1982, Broadwater County Courthouse, Broadway Street, Townsend, Montana; and Thursday, May 27, 1982, Granite County Courthouse, Sansome and Kearney Streets, Philipsburg, Montana. All hearings will start at 1 p.m. with registration beginning at 12:30 p.m.

Any interested person wishing to discuss the proposed impact aid payments formula should contact the Area or District Manager in their locality or the office of the Public Involvement Coordinator.

Written comments may be submitted through July 13, 1982.

**ADDRESSES:** Writtten comments not submitted at the hearings should be submitted to the Public Involvement Coordinator, Bonneville Power Administration, P.O. Box 12999, Portland, Oregon 97212.

**FOR FURTHER INFORMATION CONTACT:** Ms. Donna L. Geiger, Public Involvement Coordinator, 503–230–3478. Oregon callers may use the toll-free number 800–452–8429; callers in California, Idaho, Montana, Nevada, Utah, Wyoming, and Washington may use 800–547–6048.

Mr. George Gwinnutt, Lower Columbia Area Manager, Suite 288, 1500 Plaza Building, 1500 NE. Irving Street, Portland, Oregon 97208, 503–230–4551;

Mr. Ladd Sutton, Eugene District Manager, Room 206, 211 East Seventh Street, Eugene, Oregon 97401, 503–345–0311.

Mr. Ronald H. Wilkerson, Upper Columbia Area Manager, Room 561, West 920 Riverside Avenue, Spokane, Washington 99201, 509–456–2518.

Mr. Gordon H. Brandenburger, Kalispell District Manager, P.O. Box 758, Kalispell, Montana 59901, 406–755–6202.

Mr. Ronald K. Rodewald, Wenatchee District Manager, P.O. Box 741, Wenatchee, Washington 98801, 509–662–4377, extension 379.

Mr. Thomas M. Noguchi, Acting Puget Sound Area Manager, 415 First Avenue North, Room 250, Seattle, Washington 98109, 206–442–4130.

Mr. Roy Nishi, Snake River Area Manager, West 101 Poplar, Walla Walla, Washington 99362, 509–525–5500, extension 701.

Mr. Robert N. Laffel, Idaho Falls District Manager, 531 Lomax Street, Idaho Falls, Idaho 83401, 208–523–2706.

Issued in Portland, Oregon, May 17, 1982.

**Peter T. Johnson,**

*Administrator.*

[FR Doc. 82-14308 Filed 5-24-82; 8:45 am]

BILLING CODE 6450-01-M

## Federal Energy Regulatory Commission

**[Docket No. RP82-84-000]**

### Montana-Dakota Utilities Co.; Notice of Proposed Change in Rates

May 18, 1982.

Take notice that on April 30, 1982, Montana-Dakota Utilities Company (MDU), a Delaware corporation, whose mailing address is 400 North Fourth Street, Bismarck, North Dakota 58501, filed proposed changes in rates to its jurisdictional gas sales customers.

More specifically, MDU filed the following tariff sheets to its FERC Gas Tariff in which are reflected an increase in jurisdictional rates:

**Original Volume No. 4**

Twenty-First Revised Sheet No. 3A

**First Revised Volume No. 2**

Fifteenth Revised Sheet No. 10

The proposed effective date is June 1, 1982.

Increased revenues from the rates as proposed by MDU would amount to $2,938,087 annually under MDU's Rate Schedules G–1, PR–1, X–1, I–1, X–5, and X–6.

The filing indicates that MDU has experienced increases in both purchased gas costs and most other areas of its cost of service. Consequently, MDU finds it necessary to file for an increase in its jurisdictional rates.

Any person desiring to be heard or to make any protest with reference to said filing should on or before May 25, 1982, file with the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, a petition to intervene or a protest in accordance with the requirements of the Commission's Rules of Practice and Procedure (18 CFR 1.8 or 1.10). All protests filed with the Commission will be considered by it in determining the appropriate action to be taken, but will not serve to make the protestants parties to the proceeding. Any person wishing to become a party to a proceeding or to participate in any hearing therein must file a petition to intervene in accordance with the Commission's Rules of Practice and Procedure.

**Kenneth F. Plumb,**

*Secretary.*

[FR Doc. 82–14205 Filed 5–24–82; 8:45 am]

BILLING CODE 6717–01–M

## Oil Pipeline; Tentative Valuation

The Federal Energy Regulatory Commission by order issued February 10, 1978, established an Oil Pipeline Board and delegated to the Board its functions with respect to the issuance of valuation reports pursuant to Section 19a of the Interstate Commerce Act.

Notice is hereby given that a tentative valuation is under consideration for the common carrier listed below:

**1978, 1979, 1980 Consolidated Report**

*(May 20, 1982)*

Valuation Docket No. PV—1450–000

Seaway Pipeline, Inc., 370 Adams Building, Bartlesville, Oklahoma 74004

On or before June 28, 1982, persons other than those specifically designated in Section 19a(h) of the Interstate Commerce Act having an interest in this valuation may file, pursuant to rule 70 of the Interstate Commerce Commission's "General Rules of Practice" (49 CFR 1100.70), an original and three copies of a petition for leave to intervene in this proceeding.

If the petition for leave to intervene is granted the party may thus come within the category of "additional parties as the FERC may prescribe" under Section 19a(h) of the Act, thereby enabling it to file a protest. The petition to intervene must be served on the company at its address shown above and an appropriate certificate of service must be attached to the petition. Persons specifically designated in Section 19a(h) of the Act need not file a petition; they are entitled to file a protest as a matter of right under the statute.

**Francis J. Connor,**

*Administrative Officer, Oil Pipeline Board.*

[FR Doc. 82–14204 Filed 5–24–82; 8:45 am]

BILLING CODE 6717–01–M

## ENVIRONMENTAL PROTECTION AGENCY

**[OPTS 41009; TSH-FRL-2131-6]**

## Tenth Report of the Interagency Testing Committee to the Administrator; Receipt of Report and Request for Comments Regarding Priority List of Chemicals

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Notice.

**SUMMARY:** The Interagency Testing Committee (ITC), established under section 4(e) of the Toxic Substances Control Act (TSCA), transmitted its Tenth Report to the Administrator of EPA on May 10, 1982. This report, which revises and updates the Committee's priority list of chemicals, adds four chemicals to the list for priority consideration by EPA in the promulgation of test rules under section 4(a) of the Act. The four new chemicals are biphenyl, ethyltoluene, formamide, and 1,2,4-trimethylbenzene. The Tenth Report is included in this notice. The Agency invites interested persons to submit written comments on the Report, and to attend Focus Meetings to help narrow and focus the issues raised by the ITC's recommendations. Members of the public are also invited to inform EPA if they wish to be notified of subsequent public meetings on these chemicals.

**DATES:** Written comments should be submitted by June 24, 1982. Focus meetings will be held on July 12, and 13, 1982.

**ADDRESSES:** Send written submissions to: Document Control Office (TS–793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm E–409, 401 M St., SW., Washington, D.C. 20460.

Submissions should bear the Document Control Number OPTS–41009. The public record supporting this action, including comments, is available for public inspection in Rm. E–107 at the address noted above from 8:00 a.m. to 4:00 p.m. Monday through Friday, except legal holidays. Focus meetings will be held at Waterside Mall, in Rm. 3906, 401 M St., SW. Washington, D.C. If planning to attend one of the Focus Meetings and/or the subsequent public meetings on these chemicals, please notify the Industry Assistance Office at the address listed below.

**FOR FURTHER INFORMATION CONTACT:**

Douglas G. Bannerman, Acting Director, Industry Assistance Office (TS–799), Office of Toxic Substances, Environmental Protection Agency, 401 M Street, SW., Washington, D.C. 20460, Toll Free: (800–424–9065). In Washington, D.C.: (554–1404). Outside the USA: (Operator—202–544–1404).

**SUPPLEMENTARY INFORMATION:**

### I. Background

Section 4(a) of TSCA authorizes the Administrator of EPA to promulgate regulations requiring testing of chemical substances in order to develop data relevant to determining the risks that such chemical substances may present to health and the environment.

Section 4(e) of TSCA established an Interagency Testing Committee to make recommendations to the Administrator of EPA of chemical substances to be given priority consideration in proposing test rules under section 4(a). Section 4(e) directs the Committee to revise its list of recommendations at least every six months as it determines to be necessary. The total number of chemicals the ITC may designate for priority consideration within 12 months of the date of designation may not exceed 50 at any one time. EPA must either initiate rulemaking or publish in the **Federal Register** reasons for not requiring testing within that 12 months. The ITC's Tenth Report was received by the Administrator on May 10, 1982, and follows this Notice.

### II. Written and Oral Comments and Public Meetings

EPA invites interested persons to submit detailed comments on the ITC's new recommendations. The Agency is interested in receiving information concerning additional or ongoing health and safety studies on the subject chemicals as well as information relating to the human and environmental

exposure to these chemicals. Focus Meetings will be held to discuss relevant issues pertaining to the chemicals and to narrow the range of issues/effects which will be the focus of the Agency's subsequent activities in responding to the ITC recommendations. The Focus Meetings will be held July 12 and 13 at Waterside Mall, 410 M St., SW., Washington, D.C., Room 3906. These meetings are intended to supplement and expand upon written comments submitted in response to this notice. In addition to discussing concerns and data, the Focus Meetings will explore the issues of negotiated testing versus issuance of a test rule. The schedule for the Focus Meeting is the following: July 12, 9:00 a.m.—biphenyl, 1:00 p.m.—ethyltoluene; July 13, 9:00 a.m.—formamide, 1:00 p.m.—1,2,4-trimethylbenzene.

Persons wishing to attend one or more of these meetings should call the Industry Assistance Office at the toll free number listed above.

In addition to the Focus Meetings, EPA will hold public meetings on each chemical after preliminary decisions have been made on the types of testing that are needed, considering any additional information provided in the written comments and the Focus Meetings. These meetings will be several months in the future, but separate notice of these meetings will not be published later. Therefore, anyone wishing to attend these later meetings should contact EPA now at the address given for the Industry Assistance Office in order to be notified in advance of the public meetings.

All written submissions should bear the identifying Docket No. OPTS–41009.

### III. Status of List

In addition to adding four chemicals to the priority list, the Committee also noted the removal by EPA of a number of chemicals from the list based upon actions taken by the Agency. The current list contains 34 substances or categories of substances.

Dated: May 17, 1982.

**Don R. Clay,**

*Acting Assistant Administrator for Pesticides and Toxic Substances.*

## Tenth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency

*Summary*

Section 4 of the Toxic Substances Control Act of 1976 (TSCA Public Law 94–469) provides for the testing of chemicals in commerce that may present an unreasonable risk of injury to health or the environment. It also provides for the establishment of a Committee, composed of representatives from eight designated Federal agencies, to recommend chemical substances and mixtures to which the Administrator of the U.S. Environmental Protection Agency (EPA) should give priority consideration for the promulgation of testing rules.

Section 4(e)(1)(A) of TSCA directs the Committee to designate those chemical substances or mixtures to which the Administrator should respond within 12 months by either initiating a rulemaking proceeding under section (4)(a) or publishing the Administrator's reason for not initiating such as proceeding. Every 6 months, the Committee makes those revisions in the section 4(e) Priority List that it determines to be necessary and transmits them to the EPA Administrator.

As a result of its deliberations, the Committee is revising the TSCA section 4(e) Priority List by the addition of 4 entries and the removal of 14. The chemicals being added to the List are presented alphabetically, together with the types of testing recommended, as follows:

| Chemical | Recommended studies |
|---|---|
| Biphenyl | Environmental Effects and Chemical Fate: Chronic toxicity to fish and aquatic invertebrates; toxicity to aquatic macrophytes; chemical fate. |
| Ethyltoluene | Health Effects: Mutagenicity; subchronic toxicity; chemical disposition and metabolism studies to determine the biological half-life in laboratory animals and the products formed. Environmental Effects and Chemical Fate: Acute and chronic toxicity to fish and aquatic invertebrates; toxicity to aquatic macrophytes and terrestrial plants; bioconcentration; chemical fate. |
| Formamide | Health Effects: Genotoxic effects; carcinogenicity; other chronic effects. |
| 1,2,4-Trimethylbenzene | Health Effects: Subchronic/chronic effects to include neurotoxicity; reproductive effects; teratogenicity. Environmental Effects and Chemical Fate: Acute and chronic toxicity to fish and aquatic invertebrates; toxicity to aquatic macrophytes and terrestrial plants; bioconcentration; chemical fate. |

Each of the new recommendations is being designated by the Committee for action by EPA within 12 months of the date of this report.

The following entries are being removed from the List because the EPA Administrator has responded to the Committee's recommendations regarding these chemicals and categories: alkyl phthalates, benzidine-based dyes, benzyl butyl phthalate, butyl glycolyl butyl phthalate, chlorinated napthalenes, 2-chlorotoluene, chlorinated paraffins, o-diaisidine-based dyes, diethylenetriamine, fluoroalkenes, hexachloroethane, phenylenediamines, polychlorinated terphenyls, and o-tolidine-based dyes.

### TSCA Interagency Testing Committee

*Statutory Member Agencies and Their Representatives*

Council on Environmental Quality

Gordon F. Snow, Member

Department of Commerce

Bernard Greifer, Member (1)

Environmental Protection Agency

Joseph Seifter, Member
Carl R. Morris, Alternate

National Cancer Institute

Elizabeth K. Weisburger, Member and Chairperson
Richard Adamson, Aletrnate
Jerrold Ward, Alternate

National Institute of Environmental Health Sciences

Dorothy Canter, Member

National Institute for Occupational Safety and Health

Vera W. Hudson, Member
Herbert E. Christensen, Alternate

National Science Foundation

Winston C. Nottingham, Member

Occupational Safety and Health Administration

Patricia Marlow, Member

*Liaison Agencies and Their Representatives*

Consumer Product Safety Commission

Arthur Gregory
Lakshmi Mishra

Department of Agriculture

Fred W. Clayton
Homer E. Fairchild

Department of Defense

Arthur H. McCreesh

Department of the Interior

None

Food and Drug Administration

Winston deMonsabert, Vice Chairperson
Allen H. Heim

National Toxicology Program

Dorothy Canter

*Committee Staff*

Martin Greif, Executive Secretary
Norma Williams, ITC Coordinator (acting)

*Support Staff*

Alan Carpien—Office of the General Counsel, EPA
Jon Cooper (2)—Office of Toxic Substances, EPA
James Dragun (3)—Office of Toxic Substances, EPA

**References**

(1) Dr. Greifer had previously served as an Alternate and was appointed to full-member status on December 18, 1981.

(2) Dr. Cooper was appointed on December 17, 1981, to fill the vacancy created by the resignation of Dr. Gary Dickson.

(3) Dr. Dragun resigned from the Committee on April 1, 1982.

The Committee acknowledges and is grateful for the assistance and support given to it by the staff of Dynamac Corporation (technical support contractor) and numerous personnel of the EPA Office of Toxic Substances.

## Chapter 1—Introduction

1.1 *Background.* The TSCA Interagency Testing Committee (Committee) was established under section 4(e) of the Toxic Substances Control Act of 1976 (TSCA, Public Law 94-469). The specific mandate of the Committee is to recommend to the Administrator of the U.S. Environmental Protection Agency (EPA) chemical substances and mixtures in commerce that should be tested to determine their potential hazard to human health and/or the environment. TSCA specifies that the Committee's recommendations shall be in the form of a Priority List, which is to be published in the **Federal Register.** The Committee is directed by section 4(e)(1)(A) of TSCA to designate those chemicals to which the EPA Administrator should respond within 12 months by either initiating a rulemaking proceeding under section 4(a) or publishing the Administrator's reason for not initiating such a proceeding.

Every 6 months, the Committee makes those revisions in the section 4(e) Priority List that it determines to be necessary and transmits them to the EPA Administrator.

The Committee is comprised of representatives from eight statutory member agencies, five liaison agencies, and one national program. The specific representatives and their affiliations are named in the front of this report. The Committee's chemical review procedures and prior recommendations are described in previous reports (Refs. 1 through 10).

1.2 *Committee's previous reports.* Nine previous reports to the EPA Administrator have been issued by the Committee and published in the **Federal Register** (Refs. 2 through 10). Forty-nine entries (chemical substances and categories of chemicals) were designated by the Committee for priority consideration by the EPA Administrator. Five entries were removed (Ref. 10) after EPA responded to the Committee's recommendations for testing.

1.3 *Committee's activities during this reporting period.* The Committee has continued to review chemicals from its second and third rounds of scoring (see Ref. 2 for methodology) and completed a fourth scoring exercise. The chemicals selected in this exercise for review by the Committee were listed in the **Federal Register** (Ref. 11), and a public meeting was held April 22, 1982, to receive comments on these chemicals. The public was also invited to submit, in writing, comments and non-confidential unpublished data on exposure and biological effects of these chemicals.

The Committee made direct contact with more than 100 manufacturers of the chemicals being reviewed to rquest information that would be of value in its deliberations. Response by the industry has been excellent.

During this reporting period, the Committee has evaluated data on 109 chemicals for priority consideration. Four have been added to the section 4(e) Priority List; 75 were deferred from further consideration at this time.

1.4 *The TSCA section 4(e) Priority List.* Section 4(e)(1)(B) of TSCA directs the Committee to: "* * * make such revisions in the [priority] list as it determines to be necessary and * * * transmit them to the Administrator together with the Committee's reasons for the revisions." Under this authority, the Committee is revising the Priority List by adding four chemicals: biphenyl, ethyltoluene, formamide, and 1,2,4-trimethylbenzene. The testing recommended for these chemicals and the rationales for the recommendations are presented in Chapter 2 of this report.

Fourteen chemicals and categories have been removed from the Priority List because the EPA Administrator responded to the Committee's recommendations in accordance with TSCA section 4(e) requirements. The chemicals removed are indicated in Table 2 with an asterisk (*).

With the 4 designations and 14 removals in this report, 34 entries now appear on the Priority List (Table 1). The cumulative list of entries removed from the Priority List is presented in Table 2.

TABLE TABLE 1—THE TSCA SECTION 4(e) PRIORITY LIST

[April 1982]

| Entry | Date of designation |
|---|---|
| 1. Acetonitrile | April 1979. |
| 2. Acrylamide | April 1978. |
| 3. Alkyl expoxides | October 1977. |
| 4. Anile and bromo-, chloro- and/or nitroanilines. | April 1979. |
| 5. Antimony (metal) | April 1979. |
| 6. Antimony (sulfide) | April 1979. |
| 7. Antimony trioxide | April 1979. |
| 8. Aryl phosphates | April 1978. |
| 9. Biphenyl | April 1982. |
| 10. Chlorendic acid | October 1981. |
| 11. Chlorinated benzenes, mono- and di- | October 1977. |
| 12. Chlorinated benzenes, tri-, tetra-, and penta-. | October 1978. |
| 13. 4-Chlorobenzotrifluoride | October 1981. |
| 14. Cresols | October 1977. |
| 15. Cyclohexanone | April 1979. |
| 16. 1,2-Dichloropropane | October 1978. |
| 17. Ethyltoluene | April 1982. |
| 18. Formamide | April 1982. |
| 19. Glycidol and its derivatives | October 1978. |
| 20. Halogenated aklyl epoxides | April 1978. |
| 21. Hexachloro-1,3-butadiene | October 1977. |
| 22. Hexachlorocyclopentadiene | April 1979. |
| 23. Hydroquinone | November 1979. |
| 24. Isophorone | April 1979. |
| 25. Mesityl oxide | April 1979. |
| 26. 4,4'-Methylenedianiline | April 1979. |
| 27. Methyl ethyl ketone | April 1979. |
| 28. Methyl isobutyl ketone | April 1979. |
| 29. Pyridine | April 1978. |
| 30. Quinone | November 1979. |
| 31. Toluene | October 1977. |
| 32. 1,2,4-Trimethylbenzene | April 1982. |
| 33. Tris(2-chlorethyl)phosphite | October 1981. |
| 34. Xylenes | October 1977. |

TABLE 2.—CUMULATIVE REMOVALS FROM THE TSCA SECTION 4(e) PRIORITY LIST

[April 1982]

| Chemical/category | FEDERAL REGISTER | |
|---|---|---|
| | Citation | Publication date |
| 1. Alkyl phthalates* | 46 FR 53775-53777 | Oct. 30, 1981. |
| 2. Alkyltin compounds** | 47 FR 5456-5463 | Feb. 5, 1982. |
| 3. Benzidine-based dyes* | 46 FR 55005-55006 | Nov. 5, 1981. |
| 4. Benzyl butyl phthalate* | 46 FR 53775-53777 | Oct. 30, 1981. |
| 5. Butyl glycolyl butyl phthalate* | 46 FR 54487 | Nov. 2, 1981. |
| 6. Chlorinated napthalenes* | 46 FR 54491 | Nov. 2, 1981. |
| 7. Chlorinated paraffins* | 47 FR 1017-1019 | Jan. 8, 1982. |
| 8. Chloromethane | 45 FR 48524-48564 | July. 18, 1980. |
| 9. 2-Clorotolune* | 45 FR 18172-18175 | Apr. 28, 1982. |
| 10. o-Dianisidine-based dyes* | 46 FR 55005-55006 | Nov. 5, 1981. |
| 11. Dichloromethane | 46 FR 30300-30320 | June 5, 1981. |
| 12. Diethylenetriamine* | 47 FR 18386-18391 | Apr. 29, 1982. |
| 13. Flouroalkenes* | 46 FR 53704-53708 | Oct. 30, 1981. |
| 14. Hexachloroethane* | 47 FR 18175-18176 | Apr. 28, 1982. |
| 15. Nitrobenzene | 46 FR 30300-30320 | June 5, 1981. |
| 16. Phenylenediamines* | 47 FR 973-983 | Jan. 8, 1982. |
| 17. Polychlorinated terphenyls* | 46 FR 54482-54483 | Nov. 2, 1981. |

TABLE 2.—CUMULATIVE REMOVALS FROM THE TSCA SECTION 4(e) PRIORITY LIST—Continued

[April 1982]

| Chemical/category | FEDERAL REGISTER | |
|---|---|---|
| | Citation | Publication date |
| 18. o-Tolidine-based dyes* | 46 FR 55005–55006 | Nov. 5, 1981. |
| 19. 1,1,1-Trichloroethane | 46 FR 30300–30320 | June 5, 1981. |

*Removal from the section 4(e) Priority List noted in this report.
**Removal by the Committee for reconsideration.

1.5 *Availability of testing facilities and personnel.* One of the factors listed in section 4(e)(1)(A) of TSCA that the Committee must consider in making its recommendations is the reasonably foreseeable availability of facilities and personnel for performing the recommended testing. The Committee addressed this issue in its first three reports (Refs. 2 through 4). In its Third Report to the EPA Administrator, the Committee recommended that a national survey be conducted to assess the availability of personnel and testing facilities.

EPA has recently completed a national survey to assess the capacity and resources of the Nation's toxicological testing industry in relation to the demands made upon that industry with and without the additional testing requirements imposed by TSCA (Ref. 12). The report is based upon data collected during June and July 1981 and represents the latest information available on the subject. The survey found that the industry's anticipation of increased testing requirements has prompted the rapid expansion of testing facilities in recent years, and excess capacity currently exists in the toxicological testing industry.

**References**

(1) Preliminary List of Chemical Substances for Further Evaluation. Toxic Substances Control Act Interagency Testing Committee, July 1977.

(2) Initial Report to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, October 1, 1977. Published in the **Federal Register** of Wednesday, October 12, 1977, 42 FR 55026–55080. Corrections published in the **Federal Register** of November 11, 1977, 42 FR 58777–58778. The report and supporting dossiers were also published by the Environmental Protection Agency, EPA 560–10–78/001, January 1978.

(3) Second Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, April 1978. Published in the **Federal Register** of Wednesday, April 19, 1978, 43 FR 16684–16688. The report and supporting dossiers were also published by the Environmental Protection Agency, EPA 560–10–78/002, July 1978.

(4) Third Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, October 1978. Published in the **Federal Register** of Monday, October 10, 1978, 43 FR 50630–50635. The report and supporting dossiers were also published by the Environmental Protection Agency, EPA 560–10–79/001, January 1979.

(5) Fourth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, April 1979. Published in the **Federal Register** of Friday, June 1, 1979, 44 FR 31866–31889.

(6) Fifth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, November 1979. Published in the **Federal Register** of Friday, December 7, 1979, 44 FR 70664–70674.

(7) Sixth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, April 1980. Published in the **Federal Register** of Wednesday, May 28, 1980, 45 FR 35897–35910.

(8) Seventh Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, October 1980. Published in the **Federal Register** of Tuesday, November 25, 1980, 45 FR 78432–78446.

(9) Eighth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, April 1981. Published in the **Federal Register** of Friday, May 22, 1981, 46 FR 28138–28144.

(10) Ninth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, October 1981. Published in the **Federal Register** of Friday, February 5, 1982, 47 FR 5456–5463.

(11) Chemicals To Be Reviewed by the TSCA Interagency Testing Committee; Notice of Public Meeting and Request for Information. Published in the **Federal Register** of Thursday, February 25, 1982, 47 FR 8244–8246.

(12) Chemical Testing Industry Profile of Toxicological Testing. Prepared for U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances. Development Planning and Research Associates, Inc. NTIS 82–140773. EPA 560–4–81/003, October 1981.

## Chapter 2—Recommendations of the Committee

2.1 *Chemicals recommended for action by the EPA Administrator.* As provided by section 4(e)(1)(B) of TSCA, the Committee is adding the following four chemicals to the section 4(e) Priority List: biphenyl, ethyltoluene, formamide, and 1,2,4-trimethylbenzene. The designation of these entries was determined after considering the factors identified in section 4(e)(1)(A) and other available relevant information, as well as the professional judgment of Committee members.

The studies recommended for these entries and the rationales to support the recommendations are given in section 2.2 of this report. In accordance with section 4(e) of TSCA, the Committee is designating these entries for action by EPA within 12 months of the date of issuance of this Tenth Committee Report.

2.2 *Recommendations and rationales.*

2.2.a *Biphenyl.*

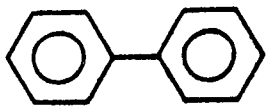
*Summary of recommended studies.* It is recommended that biphenyl be tested for the following:

A. Environmental Effects and Chemical Fate:

Chronic toxicity to fish and aquatic invertebrates
Toxicity to aquatic macrophytes
Chemical fate

*Physical and Chemical Information*

CAS Number: 92–52–4.
Structural Formula:



Empirical Formula: $C_{12}H_{10}$.
Molecular Weight: 154.
Melting Point: 71°C.

Solubility: Water, 7.5 mg/L; soluble in ethanol, diethyl ether, and benzene.

Log Octanol/Water Partition Coefficient: 4.02 (Hutchinson et al., 1980).

Description of Chemical: Colorless to pale yellow crystalline solid or flake.

*Rationale for Recommendations*

I. *Exposure information*—A. *Production/use/disposal information.* U.S. production of biphenyl in 1977 was reported in the TSCA Inventory to be between 126 million and 1.26 billion pounds (EPA, 1980a). Current annual production is estimated to be about 700 million pounds (Dow, 1981).

Biphenyl is used as as dye carrier (60 percent of production), as a heat-transfer fluid, and as a fungicide in

citrus fruit-wraps. Virtually all of the biphenyl used as a dye carrier is released from textile-finishing plant as air emission (about 5 percent) or in wastewater, where much of it is treated. As a heat-transfer fluid, biphenyl would be expected to be released to the environment through disposal. In fruit wrap, biphenyl would be partially volatilized or sorbed to citrus peel.

Biphenyl has been identified with: (1) Effluent from wood preservative, sewage treatment, and textile chemical plants; (2) influent to sewage treatment plants; (3) polyvinyl chloride smoke particulates; and (4) air in an aluminum reduction plant (Shackleford and Keith, 1976; Liao, 1978; Bjorseth, 1978). It has also been identified in the Thames River in England; in lakes, tapwater, and subterranean waters; in lake sediments in Zurich, Switzerland; and in the Merrimack River in Massachusetts (Commission of the European Communities, 1976; Giger and Schaffner, (1978). Measured concentrations of biphenyl have been detected: (1) in Athens, Georgia, drinking water at levels of 1–5 ng/L, (2) outside a specialty chemicals plant, (3) in river water at concentrations of 0.001–0.015 mg/L, (4) in river sediment at concentrations of 1–2 mg/kg, and (5) in tar balls found on the gravelly bottom of the river at undetermined concentrations (Thruston, 1978; Jungclaus et al., 1978; Guerin et al., 1978).

B. *Chemical fate information.* No studies on the overall environmental transport or persistence of biphenyl were found. This compound is expected to enter water and air, and sorb to soil and sediments. Biphenyl is expected to degrade under aerobic and anaerobic conditions. Biodegradation rates appear to be rapid in laboratory studies (Meylan and Howard, 1977; Willis and Addison, 1979). However, a study of the biodegradation of biphenyl in seawater indicated a persistence of greater than several months (Reichardt et al., 1981).

Biphenyl can react with chlorine in wastewater treatment plants to produce mono- and dichlorbiphenyls (Carlson et al., 1975). The extent of chlorination varies with pH, contact time, and the concentration of chlorine. At a pH of 5.5, which might might be expected at wastewater treatment plants, concentrations of 0.1–82 μg/L of mono- and dichlorobiphenyls were produced during 24–120 hours of contact.

II. *Biological effects of concern to human health*—The health effects of biphenyl have been studied, and no further health effects testing is recommended at this time.

III. *Environmental considerations*—A. *Short-term (acute) effects.* The acute toxicity (96-hr $LC_{50}$) reported for biphenyl is 1.5–5.3 mg/L for the fathead minnow (Kirk-Othmer, 1979; Dow, 1981). The 24-hr $LC_{50}$, the 48-hr $LC_{50}$, and the no-effect concentrations for daphnids are 27, 4.7, and 2.2 mg/L, respectively (Leblanc, 1980). The rate of photosynthesis was reduced by 50 percent in the algae *Chlamydomonas angulosa* and *Chlorella vulgaris* at 8.3 and 25 mg/L, respectively (Hutchinson et al., 1980).

B. *Long-term (subchronic/chronic) effects.* No studies on the long-term effects of biphenyl have been found for aquatic animals.

C. *Other effects (physiological/behavioral/ecosystem processes).* No studies on physiological, behavioral, or ecosystem effects of biphenyl have been found.

D. *Bioconcentration and food-chain transport.* There appears to be some bioconcentration with biphenyl. The predicted bioconcentration factor (based on the measured octanol/water partition coefficent) is 245 and agrees with the reported value of 195 for rainbow trout (Verschueren, 1977). In the two algae *C. angulosa* and *C. vulgaris,* the bioconcentration factors were 1.22 and 1.82, respectively (Hutchinson et al., 1980).

E. *Reasons for environmental effects recommendations.* The reported use/disposal pattern of biphenyl in dye-carrier applications indicates that the primary exposure of this compound is through wastewater discharge. At wastewater treatment plants, the biphenyl is expected to react with chlorine to form mono- and dichlorobiphenyls, which degrade slowly and have a high biconcentration potential. Mono- and dichlorobiphenyls are known to be toxic to aquatic organisms, and, by food-chain transport, to terrestrial organisms (EPA, 1980b). The concentrations of these chlorinated biphenyls that are produced in wastewater treatment plants are likely to exceed the EPA water quality standards for the protection of freshwater and saltwater aquatic life, which are 0.014 and 0.030 μg/L, respectively (EPA, 1980b).

The toxicity of biphenyl and its degradation products is of concern, and little is known of the fate of biphenyl in the environment. Consequently, chemical fate testing is recommended to better understand the persistence and transformations of the compound under environmental conditions. Studies of chronic toxicity to fish and aquatic invertebrates, and acute toxicity to aquatic macrophytes are recommended to further characterize the environmental effects of biphenyl.

Although biodergradation rates appear to be rapid in laboratory studies, the rate of biodegradation under environmental conditions needs to be studied more closely. In laboratory studies, acclimated cultures of microorganisms tend to degrade chemicals more rapidly than might occur in the natural environment. The study by Reichart et al. (1981) indicates that persistence of biphenyl in the environment is significantly greater than that found in the laboratory.

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2.2.b *Ethyltoluene (mixed isomers).*

*Summary of recommended studies.* The Committee recommends that ethyltoluene be tested for the following:

A. Health Effects:

Mutagenicity

Subchronic toxicity

Chemical disposition and metabolism studies to determine the biological half-life in laboratory animals and the products formed.

B. Environmental Effects and Chemical Fate:

Acute and chronic toxicity to fish and aquatic invertebrates

Toxicity to aquatic macrophytes and terrestrial plants

Bioconcentration

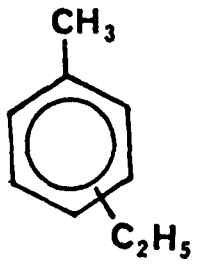
Chemical fate

*Physical and Chemical Information*

CAS Number: 25550–14–5 (mixed isomers of ortho, meta, and para).

Synonyms: Ethylmethylbenzene; Methylethylbenzene.

Structural Formula:




Empirical Formula: $C_9H_{12}$.

Molecular Weight: 120.2.

Melting Point: −85° C.

Boiling Point: 161°C.

Specific Gravity: 0.86 g/ml at 25° C (Dow, 1981).

Solubility: Water, 75 mg/L at 25° C (Dow, 1981); soluble in organic solvents.

Vapor Pressure: 3.0 mmHg at 25°(estimated; PCR, 1978).

Log Octanol/Water Partition Coefficient: 3.6 (estimated; Leo et al., 1971).

Description of Chemical: Colorless liquid.

*Rationale for Recommendations*

I. *Exposure information—A. Production and use information.* U.S. production of ethyltoluene (mixed isomers) was reported to be between 100 and 200 million pounds per year in 1977 (EPA, 1980). Ethyltoluene is used as a component of solvent products (Exxon USA, 1982; Koch Refining Co. 1982; Charter International Oil, 1982) and as an intermediate in the production of vinyltoluene (Dow, 1981).

The use of ethyltoluene in commercial solvent products provides the potential for substantial human and environmental exposures to this substance. For example a commercial solvent containing 25 percent ethyltoluene is used as the volatile component in paint (Charter International Oil, 1982.). Other general commercial solvents, used in the manufacture of printing inks and in cleaning solutions for industrial laundries, contain as much as 40 percent ethyltoluene (Exxon USA, 1982; Koch Refining Co., 1982). Sittig (1976) also reported that a $C_9$ aromatic solvent is used in wire coatings. Ethyltoluene constitutes about 2.8 percent of regular gasoline and about 1.2 percent of premium gasoline (Sanders and Maynard, 1968).

The National Occupational Hazard Survey conducted between 1972 and 1974 indicated that the number of workers potentially exposed to ethyltoluene is 16,629 (NIOSH, 1981). No threshold limit value (TLV) has been designated for ethyltoluene by ACGIH, although one manufacturer has established an in-plant exposure limit of 10 ppm (Dow, 1981).

B. *Chemical fate information.* Ethyltoluene is a moderately volatile liquid that is slightly soluble in water (75 mg/L; Mackay et al., 1980), and has been identified in water and air (Dowty et al., 1975). The isomers appear to biodegrade in water in 6–11 days in laboratory experiments (Kappeler and Wuhrmann, 1978). In the air, ethyltoluene is expected to be rapidly oxidized by hydroxyl radicals in 0.24–2.4 hours (Darnall et al., 1976). The reaction products may be major components of smog.

C. *Evidence for exposure.* The identification in air, water, food, and natural products is, at least, indirect evidence that there is environmental exposure. For instance, concentrations of ethyltoluene in air, of 1.5 and 10.0 ppb, have been found in Houston, Texas, and in Zurich, Switzerland, respectively (Bertsch et al., 1974; Grob and Grob, 1971). Ethyltoluene has been identified in white bread crust (Folkes and Gramshaw, 1977), in volatiles from the cotton plant (Hedin et al., 1975), in Australian honeys (Graddon et al., 1979), in tuna oil and turkeys fed tuna oil (Crawford and Kretsch, 1970), in the distillable organics of grenache grape oil (Stevens et al., 1967), in roast beef (Min et al., 1979), in roasted filbert nuts (Kinlin et al., 1972), and in cellulose cigarette smoke condensate (Sakuma et al., 1979).

II. *Biological effects of concern to human health—A. Acute toxicity studies.* Acute toxicity studies of ethyltoluene in rats indicated an estimated $LC_{50}$ of 4,000 ppm (Furnas and Hine, 1958). In male albino rats an oral dose of 5 ml/kg of ortho-ethyltoluene produced 100 percent mortality. The same dose of para-ethyltoluene caused 70 percent mortality (Gerarde, 1960).

B. *Subchronic toxicity studies.* No data on the subchronic toxicity of ethyltoluene were found.

C. *Mutagenicity.* No data on the mutagenic activity of ethyltoluene were found.

D. *Metabolism.* Metabolism studies of ethyltoluene have indicated that it is absorbed by rats after inhalation. Chin et al. (1980) found that 54 percent of carbon 14 ($^{14}C$) ring-labeled ethyltoluene (mixed isomers) at a concentration of 1 mg/L was absorbed by rats over a 6-hour period. Forty-two hours after the termination of the exposure, about 76 percent of the absorbed radioactivity was excreted by the rats. Some 0.32 percent of the $14_C$

label remained in the animals' bodies, but the authors did not account for the remaining 25 percent of the radioactivity (Chin et al., 1980). The biotransformation of ethyltoluene (mixed isomers) was studied in both the dog and the rat (Chin et al., 1978; 1981). Metabolites of ethyltoluene were found in the urine of both species; however, the authors did not specify the metabolic products.

E. *Reasons for health effects recommendations.* Human exposure to ethyltoluene used in commercial solvent products is of concern. Very little is known about the metabolism and health effects of the compound. Other alkyltoluenes are known to have neurotoxic effects (Hine et al., 1954). Chemical disposition and metabolism studies are recommended to determine the metabolic products of ethyltoluene, and mutagenic and subchronic toxicity studies are recommended to provide a better understanding of the toxicity of the compound. The need for chronic studies would depend on the results of the metabolic, subchronic, and mutagenic studies.

III. *Environmental considerations—A. Acute toxicity.* No studies on the short-term effects of ethyltoluene have been found for either aquatic animals or plants.

B. *Subchronic/chronic effects.* No studies on the long-term effects of ethyltoluene have been found for either aquatic animals or plants.

C. *Other effects (physiological/behavioral/ecosystem processes).* Reduction of photosynthesis in the two algae *Chlamydomonas angulosa* and *Chlorella vulgaris* was reported by Hutchinson et al. (1980) for ortho-ethyltoluene at 155 and 340 mmol/$m^3$ (19 and 49 mg/L), respectively, and for para-ethyltoluene at 450 and 400 mmol/$m^3$ (54 and 48 mg/L), respectively.

D. *Bioconcentration and food-chain transport.* The log of the octanol/water partition coefficient, estimated by Leo et al. (1971) is 3.6. By the method of Veith et al. (1980), the bioconcentration factor is calculated to be 229 for ethyltoluene (mixed isomers).

E. *Reasons for specific environmental effects recommendations.* Ethyltoluene (mixed isomers) may enter aquatic systems through solvent and other industrial usage. Although ethyltoluene was found to biodegrade in laboratory tests, the rates of biodegradation under environmental conditions need to be more closely studied. In laboratory studies, acclimated cultures of microorganisms often tend to degrade chemicals more rapidly than might occur in the natural environment. Chemical fate testing under environmental conditions is needed to better characterize the transformations and persistence of ethyltoluene in the aquatic environment.

Because of the relatively high calculated log octanol/water partition coefficient, ethyltoluene is expected to bioconcentrate in fatty tissues of living organisms. This potential for bioconcentration also increases concern for the effects of food-chain transport of ethyltoluene. For these reasons and the expected environmental entry routes, it is recommended that testing be conducted to determine the bioconcentrations of ethyltoluene.

Environmental effects testing is recommended to characterize the toxicity of ethyltoluene. No studies were found on the acute or chronic toxicity of these mixed isomers. Therefore, acute and chronic toxicity studies to fish and aquatic invertebrates and to aquatic macrophytes and terrestrial plants are recommended because of anticipated exposure and insufficient toxicity data.

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2.2.c *Formamide.*

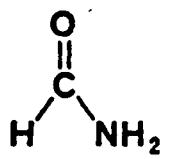
*Summary of recommended studies.* It is recommended that formamide be tested for the following:

A. Health Effects:

Genotoxic effects
Carcinogenicity
Other chronic effects

*Physical and Chemical Information*

CAS Number: 75–12–7.
Synonym: Methanamide.
Structural Formula:



Empirical Formula: $CH_3ON$.
Molecular Weight: 45.04.
Melting Point 2.6° C.
Boiling Point: 210° C (decomposes).
Vapor Pressure: 1mmHg at 70.5° C.
Log Octanol/Water Partition Coefficient: −1.64 (estimated; Leo et al., 1971).

Description of Chemical: Formamide is clear, viscous, hydroscopic liquid with a faint oder of ammonia. It is soluble in water and in most polar solvents. It is a good solvent for proteins due to its high dielectirc constant (Kirk-Othmer, 1980).

*Rationale for Recommendations*

I. *Exposure information*—A. *Production/use/disposal information.* U.S. production and importation of formamide totaled 1–11 million pounds in 1977 (EPA, 1980). Formamide has a wide variety of applications, both as a chemical intermediate and as a solvent. As an intermediate it is used in the manufacture of formic acid, hydrogen cyanide, imidazoles, pyrimidine, 1,3,5-triazine, and other compounds. As a solvent it is used in the crystallization of penicillin and dihydrostreptomycin sulfate, manufacture and processing of plastics, spinning of acrylonitrile copolymers, separation of chlorosilanes, and purification of fats and oils. It is also used as a nonaqueous electrolytic solvent, an ink solvent in felt-tipe pens, a swelling agent for cellulose, a coagulating agent for sodium silicate in grout, a softner in paper and glues, an additive in hydraulic fluids, and as a reaction medium (Kirk-Othmer, 1980; Codd, 1972; Kirk-Othmer, 1979, Merck, 1976).

The National Ococupations Hazard Survey conducted between 1972 and 1974 indicated that approximately 6,500 workers are potentially exposed to this chemical (NIOSH, 1981). The principal routes of human exposure to formamide appear to be inhalation and ingestion (Ketchen and Porter, 1979). Dermal exposure is also expected. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value/time-weighted average (TLV/TWA) of 20 ppm (30 mg/m$^3$), and a threshold limit value/short-term exposure limit (TLV/STEL) of 30 ppm (45 mg/m$^3$) (ACGIH, 1980).

B. *Chemical fate information.* Formamide hydrolyzes slowly at room temperature, Hydrolysis is accelerated by acids, bases, and elevated temperatures (Kirk-Othmer, 1980). No test data on the environmental transport of formamide have been found. It is not expected to partition to sediments or to bioaccumulate. Formamide is oxidized by activated sludge (Malaney and Gerhold, 1969), and the half-life is estimated to be less than 4 days. It has also been shown to serve as a growth medium and nitrogen source for fungi, algae, bacteria, and vascular plants (Hynes, 1970; Trotsenko and Loginova, 1973; Gresshoff, 1981; Chandra and Shethna, 1977; Fishbein, 1977).

II. *Biological effects of concern to human health*—A. *Chemical disposition/metabolism studies.* Formamide is absorbed directly through the skin of guinea pigs (Patty, 1963) and rabbits (ACGIH, 1980). Formamide hydrolyzes to its corresponding carboxylic acid both in vivo and in vitro. The site of formamide hydrolysis is the liver in the dog and rabbit, and the liver and kidneys in sheep (Bray et al., 1949).

B. *Acute toxicity.* In an acute toxicity study, the $LD_{50}$ for rats was 6.1 g/kg (Zaeva et al., 1967). In a 2-week feeding study, six rats were fed 1.5 g/kg of formamide each day. Before the 10th dose, four of the rats had died and no further dosing was administered. Two additional rats died 2 days after the 10th day (Du Pont, 1978). Formamide is classified as slightly toxic when given by the oral route (Gosselin et al., 1976). Formamide alone has no significant effects on the central nervous system of the mouse. However, it increased by 800 percent the sleeping time induced by chloral (Chanh et al., 1972). The mechanism of this effect was undefined.

C. *Carcinogenicity.* No standard bioassays on the carcinogenicity of formamide were found.

D. *Teratogenic/reproductive effects.* Teratogenic and reproductive effects have been observed in rats, mice, and rabbits at doses ranging from 0.07 g/kg to 2 g/kg. These effects include malformation of palate and limbs, syndactyly of the toes, and reversible changes in the testes (Thiersch, 1971; von Kreybig, 1967; Chanh et al., 1973; Gleich, 1974). Formamide administered orally to pregnant rats (in 2 g/kg doses) on the 7th day of gestation led to resorption of one-half of all implanted rat fetuses, with stunting of 26 percent of the survivors (Thiersch, 1962). When formamide was administered to pregnant rabbits by gavage (70 μl/kg doses) from the 6th to the 18th day of gestation, embroyotoxic and weak teratogenic effects such as cleft palate and skeletal malformations were noted (Merkle and Zeller, 1980). In mice, after two dermal applications of 76 μg/animal, a 36 percent increase in the rate of malformation of the fetus was observed (Gleich, 1974).

E. *Mutagenicity.* Formamide was tested (as one of 14 solvents) for compatibility with the Salmonella mutagenicity test (Maron et al., 1981). The compound was nonmutagenic in the Ames assay, using the TA 100 strain. The investigators suggest that formamide may be used as a solvent in place of dimethylsulfoxide (DMSO). Other strains and concentrations were not tested. This compound has been described as "inactive in vivo" and also inactive in a cell transformation test using rat embryo cells infected with Rauscher leukemia virus (Freeman et al., 1973).

Formamide can denature and renature DNA at room temperature (Gillespie and Gillespie, 1971; McConaughy et al., 1969; Roussel and Chabbert, 1978). Exposure of roots of *Vicia faba* to the compound did not increase the chromatid aberration rate (Nicoloff, 1976). Mitotic anomalies were observed in the chick (Messier, 1976).

F. *Health effects recommendations.* Formamide is widely used as a chemical intermediate and as a solvent. Worker

exposure is likely from its use in grout, inks, glues, and paper. Although mutagenicity testing of formamide has been conducted, the data are insufficient to determine its genotoxic potential. In several studies, teratogenic effects have been observed in laboratory animals. Very little is known about the chronic toxicity, and no data were found on carcinogenicity. Based on these considerations, formamide is recommended for appropriate genotoxicity tests in conjunction with carcinogenicity and other chronic effects tests.

III. *Environmental considerations*—Because formamide is highly soluble in water and has low volatility, it is expected to partition into the aqueous compartment with no bioaccumulation. Furthermore, the compound has been shown to be readily biodegraded by activated sludge (Malaney and Gerhold, 1969) and to serve as a growth medium and nitrogen source for bacteria, algae, fungi, and vascular plants (Chandra and Shethna, 1977; Hynes, 1970; Trotsenko and Loginova, 1973; Fishbein, 1977; Gresshoff, 1981). For these reasons, formamide is not exptected to persist in the environment and no environmental testing is recommended.

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2.2.d *1,2,4-Trimethylbenzene.*

*Summary of recommended studies.* It is recommended that 1,2,4-trimethylbenzene be tested for the following:

A. Health Effects:

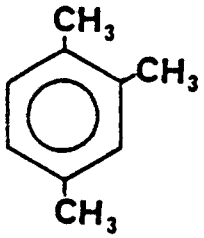
Subchronic/chronic effects to include neurotoxicity
Reproductive effects
Teratogenicity

B. Environmental Effects and Chemical Fate:

Acute and chronic toxicity to fish and aquatic invertebrates
Toxicity to aquatic macrophytes and terrestrial plants
Bioconcentration
Chemical fate

*Physical and Chemical Information*

CAS Number: 95–63–6.
Synonym: Pseudocumene.
Structural Formula:




Empirical Formula: $C_9H_{12}$.
Molecular Weight: 120.2.
Specific Gravity: 0.889.

Freezing Point: −43.8°C.
Boiling Point: 169–171°C.
Vapor Pressure: 2 mmHg at 25°C (estimated).
Solubility: Water, 57 mg/L; soluble in ethanol, benzene, and ether.
Log Octanol/Water Partition Coefficient: 3.6 (estimated; Leo et al., 1971).
Description of Chemical: Colorless liquid.

*Rationale for Recommendations*

I. *Exposure information*—A. *Production/use/disposal information.* Current U.S. production of 1,2,4-trimethylbenzene is in excess of 10–50 million pounds per year (EPA, 1980; personal communication with manufacturers). The principal use of the isolated compound is as an intermediate in the manufacture of trimellitic anhydride, dyes, and pharmaceuticals (Hawley, 1977). The trimellitic anhydride is used in the production of plasticizers, alkyd resins, unsaturated polyesters, and other industrial chemicals (Cerf et al., 1980). Trimethylbenzene can be used as an ultraviolet stabilizer in plastics. Dyshinevich (1979) reported that trimethylbenzene is released from polymeric material, thus suggesting migration from the polymers. The isolated compound is also used as a dye-carrier solvent and as a scintillation-counter solvent (SPPC, 1982).

In addition to the amount produced as an isolated compound, as reported in the TSCA Inventory (EPA, 1980), 1,2,4-trimethylbenzene is produced as a component of the $C_9$ aromatic fraction of petroleum (Sittig, 1976). This fraction is used as a general solvent (e.g., in paint thinners; Cerf et al., 1980) or as a component of gasoline (SPPC, 1982; Lee et al., 1974). This increases the potential for human and environmental exposure to the compound through solvent usage and disposal, and through gasoline evaporation during transportation, storage, and spills.

The National Occupational Hazard Survey conducted between 1972 and 1974 indicated that approximately 3,000 workers are potentially exposed to this chemical (NIOSH, 1981). The most probable routes of exposure are by inhalation of the vapor or mist and by skin contact with the liquid (Lazarew, 1929; Gerarde, 1960). A threshold limit value of 25 ppm and a short-term exposure limit of 35 ppm have been recommended by ACGIH (1980).

B. *Chemcial fate information.* 1,2,4-Trimethylbenzene is slightly soluble in water (57 mg/L; Mackay et al., 1980). It appears to be biodegraded in water in 7 days in a laboratory experiment (Kappeler and Wuhrmann, 1978). 1,2,4-trimethylbenzene is expected to partition to air, where it will oxidize rapidly (Kuntz et al., 1973; Darnall et al., 1976); the reaction products can be a component in smog. It is a constitutent of the water-soluble component of crude oil (Lee et al., 1974) and refined gasoline (Sanders and Maynard, 1968).

C. *Evidence for exposure.* The identification of 1,2,4-trimethylbenzene in air is indirect evidence that there is environmental exposure. Examples of concentrations of 1,2,4-trimethylbenzene reported in air are: 9.0 ppb in Zurich, Switzerland (Grob and Grob, 1971), 1–13 ppt in a rural Australian town (Nelson et al., 1977), and unspecified concentrations in Houston, Texas (Bertsch et al., 1974), and in six Soviet cities (Ioffe et al., 1978). The compound has also been observed in cooked chicken meat volatiles (Nonaka et al., 1967); fermented eggs (Bullard et al., 1978); volatiles from roasted filberts (Kinlin et al., 1972); and volatiles from roast beef (Min et al., 1979).

II. *Biological effects of concern to human health*—A. *Acute/short term effects.* The acute toxicity of the compound has been well studied (Gerarde, 1960; Cameron, 1938; Litton Bionetics, 1976; Lazarew, 1929; Dyshinevich, 1979). It has been shown to have a moderate to low order of acute toxicity by various routes of administration; i.e., oral, intraperitoneal, inhalation, and subcutaneous in rats, mice, and guinea pigs.

Rats and mice were exposed by inhalation at 2,000 ppm for 8 hours per day for 14 days, and no adverse effects were reported (Cameron, 1938). In another study, eight rats were exposed by inhalation to the compound at 1,000 and 2,000 ppm for 15 and 12 exposures of 6 hours each, respectively (Gage, 1970). At the higher concentration, nose and eye irritation, respiratory difficulty, lethargy, tremors, and low weight increase were observed; however, at both concentrations, blood test results were normal and organs were also normal at necropsy.

B. *Subchronic effects.* Dyshinevich (1979) reported effects on the functional state of the central nervous system, blood enzyme composition, and the liver of rats exposed by continuous inhalation for 4 months to 20 $mg/m^3$ (4 ppm) of 1,2,4-trimethylbenzene. These effects were not observed at 0.4 ppm. No histopathological end-points were reported.

C. *Carcinogenity/chronic effects.* A 2-year feeding study in rats designated to assess the carcinogenic potential of 1,2,4-trimethylbenzene was cancelled before testing was initiated (EPA, 1981). No data on carcinogenicity or other chronic effects were found in the literature.

D. *Mutagenicity.* The genetic activity of 1,2,4-trimethylbenzene was tested by microbial assay with and without addition of mammalian metabolic activation. It was tested and found negative in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100, and in *Saccharomyces cerevisiae* strain D4 (Litton Bionetics, 1977).

E. *Teratogenicity and reproductive effects.* No data on teratogenic or reproductive effects were found.

F. *Observations in humans.* Battig et al. (1956) studied 27 workers exposed for several years to the paint thinner "Fleet-X-DV-99," the hydrocarbon vapor concentration of which ranged from 10 to 60 ppm. The paint thinner contained trimethylbenzene (50 percent 1,2,4- and 30 percent 1,3,5-trimethylbenzene) and a small proportion of benzene. This exposure caused blood coagulation disturbances, asthmatic bronchitis, hypochromic anemia, headache, fatigue, and drowsiness. Dowty and Laseter (1976) reported trimethylbenzene (unspecified isomers) in eleven maternal-cord blood samples collected at birth. The purpose of the study was to identify the presence of transplacentally-acquired compounds, the source of which was not identified.

G. *Rationale for health effects recommendations.* In view of the exposure potential of 1,2,4-trimethylbenzene and the lack of sufficient information on subchronic and chronic health effects, the Committee recommends that appropriate subchronic/chronic testing, to include neurotoxicity, be conducted. In addition, teratogenic and reproductive effects should be studied.

Three trimethylbenzene isomers and a mixture of the isomers are reported to be in commerce in the United States (EPA, 1980). Of these 1,2,4-trimethylbenzene has the largest production volume and potential for exposure; therefore, it was singled out for this testing recommendation. A preliminary review of health data on the other isomers discloses that, biologically, all three isomers may behave similarly. Consequently, the Committee recommends that EPA study the testing needs of the other isomers for both health and environmental effects, while giving priority consideration to 1,2,4-trimethylbenzene.

III. *Environmental considerations*—A. *Short-term (acute) effects.* The 24-, 48-, 72-, and 96-hour $CL_{50}$ values for an

isomer of 1,2,4-trimethylbenzene (1,3,5-trimethylbenzene) to goldfish were 20.57, 16.17, 13.65, and 12.52 mg/L, respectively (Brenniman et al., 1976). The 24-, 48-, and 96-hour $LC_{50}$ values for 1,2,4-trimethylbenzene to the marine amphipod *Elasmopus pectenicrus* were 5.23, 4.91, and 4.35 mg/L, respectively (Lee and Nicol, 1978).

B. *Long-term (subchronic/chronic effects.* No studies on the long-term effects of 1,2,4-trimethylbenzene have been found for either aquatic animals or plants.

C. *Other effects (physiological/behavioral/ecosystem/processes).* 1,2,4-trimethylbenzene caused complete inhibition of nitrogen fixation in arctic marine sediments, and partial inhibition of carbon dioxide production from glucose (Knowles and Wishart, 1977). Donahue et al. (1977) reported that a 15 percent saturated solution of 1,2,4-trimethylbenzene in seawater reduced the swimming activity of the larvae of the barnacle *Balanus amphitrite.* Increased levels of the microsomal enzymes were observed in the southern armyworm after oral treatment with the compound (Brattsten and Wilkinson, 1973).

D. *Bioconcentration and food-chain transport.* The log of the octanol/water partition coefficient for 1,2,4-trimethylbenzene, estimated by Leo et al. (1971), is 3.6. By the method of Veith et al. (1980), the bioconcentration factor is calculated to be 229.

E. *Rationale for environmental effects recommendations.* 1,2,4-Trimethylbenzene may enter aquatic systems through solvent and other industrial usage. Although trimethylbenzene was found to biodegrade in laboratory tests, the rates of biodegradation under environmental conditions need to be studied more closely. In laboratory studies, acclimated cultures of micro-organisms often tend to degrade chemicals more rapidly than might occur in the natural environment. Chemical fate testing under environmental conditions is needed to better characterize its transformations and persistence in the aquatic environment.

Because of the relatively high calculated log octanol/water partition coefficient, 1,2,4-trimethylbenzene is expected to bioconcentrate in the fatty tissues of living organisms. This potential for bioconcentration also increases the concern for the effects of food-chain transport. For these reasons and the expected environmental release, it is recommended that testing be conducted to determine the bioconcentration of 1,2,4-trimethylbenzene.

Environmental effects testing is recommended to characterize the toxicity of 1,2,4-trimethylbenzene. The acute studies that have been conducted on its toxicity are not adequate to make an environmental assessment. Goldfish are not considered a sensitive species, and the relative sensitivity of *Elasmopus* has not been studied. No studies on the chronic toxicity of this compound were found. Therefore, studies on the acute and chronic toxicity to fish and aquatic invertebrates, and toxicity to aquatic macrophytes and terrestrial plants are recommended because of anticipated exposure and insufficient toxicity data.

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[FR Doc. 14200 File 5–24–82; 8:45 am]

BILLING CODE 6560–50–M

## FEDERAL COMMUNICATIONS COMMISSION

### Forms Under Review by the Office of Management and Budget

May 17, 1982.

Public Information Collection Requirements Submitted to Office of Management and Budget for Review.

On May 12 the Federal Communications Commission submitted the following public information collection requirement to OMB for review and clearance under the Paperwork Reduction Act of 1980, Pub. L. 96–511.

Copies of this submission are available from Richard D. Goodfriend, Agency Clearance Officer, (202) 632–7513. Comments should be sent to Edward H. Clarke, Office of Management and Budget, OIRA, Room 3201 NEOB, 726 Jackson Place, NW., Washington, D.C. 20503.

Title: Annual Report of Cable Television Systems

Form No.: FCC 325

2 forms:

Schedule 1—Community Unit Data

Schedule 2—Physical System Data

Action: Extension

Burden: 20,000 Responses; 80,000 Hours

Federal Communications Commission.

**William J. Tricarico,**

*Secretary.*

[FR Doc. 82–14149 Filed 5–24–82; 8:45 am]

BILLING CODE 6712–01–M

## FEDERAL MARITIME COMMISSION

### Agreements Filed

The Federal Maritime Commission hereby gives notice that the following agreements have been filed with the Commission for approval pursuant to section 15 of the Shipping Act, 1916, as amended (39 Stat. 733, 75 Stat. 763, 46 U.S.C. 814).

Interested parties may inspect and obtain a copy of each of the agreements and the justifications offered therefor at the Washington Office of the Federal Maritime Commission, 1100 L Street, NW., Room 10327; or may inspect the agreements at the Field Offices located at New York, N.Y.; New Orleans, Louisiana; San Francisco, California; Chicago, Illinois; and San Juan, Puerto Rico. Interested parties may submit comments on each agreement, including requests for hearing, to the Secretary, Federal Maritime Commission, Washington, D.C. 20573, on or before June 14, 1982. Comments should include facts and arguments concerning the approval, modification, or disapproval of the proposed agreement. Comments shall discuss with particularity allegations that the agreement is unjustly discriminatory or unfair as between carriers, shippers, exporters, importers, or ports, or between exporters from the United States and their foreign competitors, or operates to the detriment of the commerce of the United States, or is contrary to the public interest, or is in violation of the Act.

A copy of any comments should also be forwarded to the party filing the agreements and the statement should indicate that this has been done.

Agreement No.: 9988–14.

Filing Party: Howard A. Levy, Esquire, Suite 727, 17 Battery Place, New York, New York 10004.

Summary: Agreement No. 9988–14 modifies the geographical scope of the Continental/U.S. Gulf Freight Association Agreement No. 9988 to reduce the range of U.S. ports covered from the Brownsville, Texas—Cape Canaveral, Florida range to the Brownsville, Texas—Key West, Florida range.

Agreements Nos.: 10392–2 and 10410–1

Filing Party: Ronald C. Rasmus, President, American Atlantic Lines, One World Trade Center, Suite 1067, New York, New York 10048.

Summary: Agreements Nos. 10392 and 10410 authorize discussions between American Atlantic Lines and Frota Amazonica, S.A. regarding the establishment of subsequent agreements for cargo distribution and traffic rationalization in the trades between the Brazilian Amazon Basin and the U.S. Atlantic and Gulf ranges respectively. The subject modifications extend the term of their respective agreements for a period of six months to expire with January 10, 1983, and eliminates obsolete language within the agreements. Agreement No. 10410–1 also provides for reporting the substance of all discussions to the Federal Maritime Commission within 30 days.

By Order of the Federal Maritime Commission.

Dated: May 19, 1982.

**Francis C. Hurney,**

*Secretary.*

[FR Doc. 82–14157 Filed 5–24–82; 8:45 am]

BILLING CODE 6730–01–M

### Independent Ocean Freight Fowarder License; Applicants

Notice is hereby given that the following applicants have filed with the Federal Maritime Commission applications for licenses as independent ocean freight forwarders pursuant to section 44(a) of the Shipping Act, 1916 (75 Stat. 522 and 46 U.S.C. 841(c)).

Persons knowing of any reason why any of the following applicants should not receive a license are requested to communicate with the Director, Bureau of Certification and Licensing, Federal Maritime Commission, Washington, D.C. 20573.

Armco International Shipping Corp., 9341 S.W. 53rd Street, Miami, FL 33165
Officers: Silvia A. Escobar, President/Sole Stockholder

By the Federal Maritime Commission.

Dated: May 19, 1982.

**Francis C. Hurney,**

*Secretary.*

[FR Doc. 82–14159 Filed 5–24–82; 8:45 am]

BILLING CODE 6730–01–M

**[Independent Ocean Freight Forwarder License No. 1620]**

### Trade Express, Inc.; Order of Revocation

On April 12, 1982, Trade Express, Inc., P.O. Box 91090, World Way Postal Center, Los Angeles, CA 90009 surrendered its Independent Ocean Freight Forwarder License No. 1620 for revocation.

Therefore, by virtue of authority vested in me by the Federal Maritime Commission as set forth in Manual of Orders, Commission Order No. 1 (Revised), § 10.01(e) dated November 12, 1981;

It is ordered, that Independent Ocean Freight Forwarder License No. 1620 issued to Trade Express, Inc. be revoked effective April 12, 1982, without prejudice to reapplication for a license in the future.

It is further ordered, that a copy of this Order be published in the Federal Register and served upon Trade Express, Inc.

**Albert J. Klingel, Jr.,**

*Director, Bureau of Certification and Licensing.*

[FR Doc. 82-14158 Filed 5-24-82; 8:45 am]

BILLING CODE 6730-01-M

## Security for the Protection of the Public Financial Responsibility To Meet Liability Incurred for Death or Injury to Passengers or Other Persons on Voyages; Issuance of Certificate [Casualty]

Notice is hereby given that the following have been issued a Certificate of Financial Responsibility to Meet Liability Incurred for Death or Injury to Passengers or Other Persons on Voyages pursuant to the provisions of Section 2, Pub. L. 89-777 (80 Stat. 1356, 1357) and Federal Maritime Commission General Order 20, as amended (46 CFR Part 540):

Schiffahrtsgesellschaft MS Frankfurt GmbH & Co., Peter Deilmann-Reederei, AM Hafensteig 19, 2430 Neustadt/Holstein, West Germany.

Dated: May 20, 1982.

**Francis C. Hurney,**

*Secretary.*

[FR Doc. 82-14178 Filed 5-24-82; 8:45 am]

BILLING CODE 6730-01-M

**[Independent Ocean Frieght Forwarder License No. 1840]**

## Joseph R. Elia; Order of Revocation

Section 44(c), Shipping Act, 1916, provides that no independent ocean freight forwarder license shall remain in force unless a valid bond is in effect and on file with the Commission. Rule 510.15(d) of Federal Maritime Commission General Order 4 further provides that a license shall be automatically revoked for failure of a licensee to maintain a valid bond on file.

The bond issued in favor of Joseph R. Elia, 27 Park Row, New York, NY 10007 was cancelled effective May 19, 1982.

The letter dated April 23, 1982 addressed to Joseph R. Elia at the above address advising that Independent Ocean Freight Forwarder License No. 1840 would be automatically revoked unless a valid surety bond was filed with the Commission was returned by the post office as unclaimed.

Joseph R. Elia has failed to furnish a valid bond.

By virtue of authority vested in me by the Federal Maritime Commission as set forth in Manual of Orders, Commission Order No. 1 (Revised), section 10.01(f) dated November 12, 1981;

Notice is hereby given, that Independent Ocean Freight Forwarder License No. 1840 be and is hereby revoked effective May 19, 1982.

It is ordered, that Independent Ocean Freight Forwarder License No. 1840 issued to Joseph R. Elia be returned to the Commission for cancellation.

It is further ordered, that a copy of this Order be published in the Federal Register and served upon Joseph R. Elia.

**Albert J. Klingel, Jr.,**

*Director, Bureau of Certification and Licensing.*

[FR Doc. 82-14207 Filed 5-24-82; 8:45 am]

BILLING CODE 6730-01-M

## FEDERAL RESERVE SYSTEM

### Agency Forms Under Review

May 18, 1982.

### Background

When executive departments and agencies propose public use forms, reporting, or recordkeeping requirements, the Office of Management and Budget (OMB) reviews and acts on those requirements under the Paperwork Reduction Act (44 U.S.C. Chapter 35). Departments and agencies use a number of techniques including public hearings to consult with the public on significant reporting requirements before seeking OMB approval. OMB in carrying out its responsibilities under the act also considers comments on the forms and recordkeeping requirements that will affect the public. Reporting or recordkeeping requirements that appear to raise no significant issues are approved promptly. OMB's usual practice is not to take any action on proposed reporting requirements until at least ten working days after notice in the Federal Register, but occasionally the public interest requires more rapid action.

### List of Forms Under Review

Immediately following the submission of a request by the Federal Reserve for OMB approval of a reporting or recordkeeping requirement, a description of the report will be published in the Federal Register. This information will contain the name and telephone number of the Federal Reserve Board clearance officer (from whom a copy of the form and supporting documents is available). The entries will be grouped by type of submission—i.e., new forms, revisions, extensions (burden change), extensions (no change), and reinstatements. Each report description contains the following information:

—The title of the form.
—The Federal Reserve report form number, if applicable.
—How often the form must be filled out.
—Who will be required or asked to report.
—The standard industrial classification (SIC) codes, referring to specific respondent groups that are affected.
—Whether small businesses or organizations are affected.
—A description of the Federal budget functional category that covers the information collection.
—An estimate of the number of responses.
—An estimate of the total number of hours needed to fill out the form.
—An estimate of the cost to the Federal Government.
—An estimate of the cost to the public.
—The number of forms in the request for approval.
—An indication of whether section 3504(h) of Pub. L. 96-511 applies.
—The name, address, and telephone number of the person or office responsible for OMB review, and
—An abstract describing the need for and uses of the information collection.

### Comments and Questions

Copies of the proposed forms and supporting documents may be obtained from the Federal Reserve Board clearance officer whose name, address, and telephone number appear below. The supporting documents consist of the request for clearance (SF 83), supporting statement, instructions, transmittal letters, and other documents that are submitted to OMB for review.

**FOR FURTHER INFORMATION CONTACT:**

Federal Reserve Board Clearance Officer—William R. Jones—Financial Reports Section, Division of Research and Statistics, Board of Governors of the Federal Reserve System, Washington, D.C. 20551, (202-452-2983)

OMB Reviewer—Richard Sheppard—Office of Information and Regulatory Affairs, Office of Management and

Budget, New Executive Office Building, Room 3208, Washington, D.C. 20503, (202-395-6880)

**New Form Under Review**

1. Weekly Report of Overnight Eurodollars for Selected Money Market Mutual Funds
FR 2051d
Weekly
Money market mutual funds that have $25 million or more in overnight Eurodollar deposits
SIC: 672
Small businesses are not involved
General Government: 572 responses; 97 hours; $500 Federal cost; $1,459 public cost; 1 form; not applicable under sec. 3504(h)

This report collects information on overnight Eurodollar deposits held by money market mutual funds at foreign branches of U.S. depository institutions. These data are used by the Federal Reserve to make adjustments in components of the monetary aggregates (M2 and M3) to prevent double counting of these deposits in the aggregates.

**Revised Forms Under Review**

1. Survey of Terms of Bank Lending (STBL) to Business; STBL to Farmers; Prime Rate Supplement
FR 2028A, FR 2028B, FR 2028A-S
Quarterly
Sample of insured commercial banks
SIC: 602
Small business
General government: 4,080 responses; 6,507 hours; $88,314 Federal cost; $97,605 public cost; 3 forms; not applicable under sec. 3504(h)

The FR 2028A and FR 2028B reports collect information on interest rates and selected nonprice terms of lending on individual loans to business and farmers from a sample of insured commercial banks. The FR 2028A-S report collects the banks' prime interest rate for each day covered by the 2028A survey. Current analysis of the data provides a basis for monetary policy purposes.

2. Survey of Debits To Demand and Savings Deposit Accounts
FR 2573
Monthly
Sample of commercial banks that are members of the Federal Reserve System
SIC: 602pt.
Small business
General government: 3,600 responses; 1,800 hours; $68,963 Federal cost; $36,000 public cost; 1 form; not applicable under sec. 3504(h)

Report collects information on debits to demand and savings deposit accounts from a sample of member banks. Debits information is used in formulating banking and credit policies. These data are also used in conjunction with other data to interpret money-stock movements and to determine the turnover rate for various sectors of the economy.

**Technical Revision to the Federal Register**

It was determined that the following report was not subject to the requirements of 44 U.S.C. Chapter 35 3507 because the respondent panel size was less than ten, therefore exempting the report from OMB approval.

Agreement of Foreign Nonmember Bank in Connection With Extension of Credit to Broker-Dealers
FR T-2
As per amendment to section 6(h) of Regulation T
(12 CFR 220.6(h)), May 12, 1982.

Board of Governors of the Federal Reserve System, May 18, 1982.

**Dolores S. Smith,**

*Assistant Secretary of Board.*

[FR Doc. 82-14131 Filed 5-24-82; 8:45 am]

BILLING CODE 6210-01-M

## Acquisition of Bank Shares by Bank Holding Company

The company listed in this notice has applied for the Board's approval under section 3(a)(3) of the Bank Holding Company Act (12 U.S.C. 1842(a)(3)) to acquire voting shares or assets of a bank. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors, or at the Federal Reserve Bank indicated for the application. With respect to the application, interested persons may express their views in writing to the address indicated. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

A. **Secretary, Board of Governors of the Federal Reserve System,** Washington, D.C. 20551:

1. *Guaranty, Inc.*, Beloit, Kansas; to acquire 24.8 percent of the voting shares or assets of Delphos Inc., Delphos, Kansas. Comments on this application must be received not later than June 18, 1982.

Board of Governors of the Federal Reserve System, May 19, 1982.

**Dolores S. Smith,**

*Assistant Secretary of the Board.*

[FR Doc. 82-14151 Filed 5-24-82; 8:45 am]

BILLING CODE 6210-01-M

## Formation of Bank Holding Companies

The companies listed in this notice have applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become bank holding companies by acquiring voting shares and/or assets of a bank. The factors that are considered in acting on the applications are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

Each application may be inspected at the offices of the Board of Governors, or at the Federal Reserve Bank indicated for that application. With respect to each application, interested persons may express their views in writing to the address indicated for that application. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

A. **Federal Reserve Bank of Atlanta** (Robert E. Heck, Vice President), 104 Marietta Street, NW., Atlanta, Georgia 30303:

1. *West Baton Rouge Bancshares, Inc.*, Port Allen, Louisiana; to become a bank holding company by acquiring 80 percent of the voting shares of Bank of West Baton Rouge, Port Allen, Louisiana. Comments on this application must be received not later than June 18, 1982.

B. **Federal Reserve Bank of Minneapolis** (Lester G. Gable, Vice President) 250 Marquette Avenue, Minneapolis, Minnesota 55480:

1. *American Bancorporation of Danube, Inc.*, Edison, Minnesota; to become a bank holding company by acquiring an additional 76 percent of the voting shares of American State Bank of Danube, Danube, Minnesota. Applicant currently owns 24 percent of the bank shares. Comments on this application must be received not later than June 18, 1982.

2. *Headwaters Bancorp., Inc.*, Land O'Lakes, Wisconsin; to become a bank holding company by acquiring 100 percent of the voting shares of Headwaters State Bank, Land O'Lakes, Wisconsin. Comments on this

application must be received not later than June 18, 1982.

Board of Governors of the Federal Reserve System, May 19, 1982.

**Dolores S. Smith,**

*Assistant Secretary of the Board.*

[FR Doc. 82-14153 Filed 5-24-82; 8:45 am]

BILLING CODE 6210-01-M

## National City Corp.; Acquisition of Bank

National City Corporation, Cleveland, Ohio, has applied for the Board's approval under section 3(a)(5) of the Bank Holding Company Act (12 U.S.C. 1842(a)(5) to merge with Ohio Citizens Bancorp, Inc., Toledo, Ohio. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

National City Corporation, Cleveland, Ohio, is also engaged in the following nonbank activities: underwriting credit life, accident and health insurance; performing functions that may be performed by a trust company; engaging in floor plan financing of new and used car dealers; making loans such as would be made by a finance company. In addition to the factors considered under section 3 of the Act (banking factors), the Board will consider the proposal in the light of the company's nonbanking activities and the provisions and prohibitions in section 4 of the Act (12 U.S.C. 1843).

The application may be inspected at the offices of the Board of Governors or the Federal Reserve Bank of Cleveland. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than June 18, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, May 19, 1982.

**Dolores S. Smith,**

*Assistant Secretary of the Board.*

[FR Doc. 82-14152 Filed 5-24-82; 8:45 am]

BILLING CODE 6210-01-M

# FEDERAL TRADE COMMISSION

## Equal Access to Justice Act; Information Collection Requirement

**AGENCY:** Federal Trade Commission.

**ACTION:** Application to OMB under the Paperwork Reduction Act (44 U.S.C. 3501 *et seq.*) for clearance of the Commission's Rules Implementing the Equal Access to Justice Act.

**SUMMARY:** Under the Equal Access to Justice Act small businesses and individuals may apply for reimbursement of attorneys fees and costs incurred during adjudicative proceedings before the Commission. The Commission's Rules implementing the Equal Access to Justice Act (46 FR 48910, Oct. 5, 1981) contain a paperwork requirement in the form of the application for benefits. Although no form is required, the applicant must submit financial information from which eligibility for, and the amount of, benefits is determined. The Commission is now seeking OMB clearance for the information collection requirement of the rules.

**DATES:** Comments on the application must be submitted on or before June 24, 1982.

**ADDRESS:** Send comments to Ms. Nell Minow, Office of Information and Regulatory Affairs, Office of Management and Budget, New Executive Office Building, Room 3228, Washington, D.C. 20503. Copies of this application may be obtained from: Public Reference Branch, Room 130, Federal Trade Commission, Washington, D.C. 20580.

**FOR FURTHER INFORMATION CONTACT:** Carl D. Hevener, OMB Liaison Officer, Federal Trade Commission, Washington, D.C. 20580, (202) 523-3373.

**Carol M. Thomas,**

*Secretary.*

[FR Doc. 82-14166 Filed 5-24-82; 8:45 am]

BILLING CODE 6750-01-M

**[Docket No. 82F-0144]**

## Cook Paint & Varnish Co.; Filing of Food Additive Petition

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing that Cook Paint & Varnish Co. has filed a petition proposing that the food additive regulations be amended to provide for the safe use of triglycidyl isocyanurate as a component of coatings for storage tanks containing dry food.

**FOR FURTHER INFORMATION CONTACT:** John L. Herrman, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St., SW., Washington, D.C. 20204; 202-472-5690.

**SUPPLEMENTARY INFORMATION:** Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5), 72 Stat. 1786 (21 U.S.C. 348(b)(5))), notice is given that a petition (FAP 1B3580) has been filed by Cook Paint & Varnish Co., P.O. Box 389, Kansas City, MO 64141, proposing to amend § 177.2420 *Polyester resins, cross-linked* (21 CFR 177.2420) to provide for the safe use of triglycidyl isocyanurate (CAS Reg. No. 2451-62-9) as a component of coatings for storage tanks containing dry foods.

The potential environmental impact of this action is being reviewed. If the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the **Federal Register** in accordance with 21 CFR 25.40(c) (proposed December 11, 1979; 44 FR 71742).

Dated: May 18, 1982.

**Sanford A. Miller,**

*Director, Bureau of Foods.*

[FR Doc. 82-14145 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

# DEPARTMENT OF HEALTH AND HUMAN SERVICES

## Food and Drug Administration

**[Docket No. 82N-0058; DESI 11300]**

## Combination Drugs Containing Chlorzoxazone and Acetaminophen; Opportunity for Hearing on Proposal To Withdraw Approval of New Drug Application

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice.

**SUMMARY:** This notice reclassifies combination drug products containing chlorzoxazone and acetaminophen to lacking substantial evidence of effectiveness, proposes to withdraw approval of the new drug application, and offers an opportunity for a hearing on the proposal.

**DATE:** Hearing requests due on or before June 24, 1982.

**ADDRESSES:** Communications in response to this notice should be identified with the reference number DESI 11300 and the Docket number appearing in the heading of this notice, and addressed to the appropriate office named below.

Requests for Hearing: Dockets Management Branch, (HFA-305), Rm. 4-65, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD–310), Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Herbert Gerstenzang, Bureau of Drugs (HFD–32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3650.

**SUPPLEMENTARY INFORMATION:** In a notice (DESI 11300) published in the **Federal Register** of September 11, 1969 (34 FR 14299), the Food and Drug Administration (FDA) announced its conclusion that the following drug products are possibly effective for their labeled indications.

NDA 11–529; Parafon Tablets containing chlorzoxazone 125 milligrams (mg) and acetaminophen 300 mg; previously marketed by McNeil Pharmaceutical, Spring House, PA 19477; and

Parafon Forte Tablets containing chlorzoxazone 250 mg and acetaminophen 300 mg; McNeil Pharmaceutical.

Other drugs named in the September 11, 1969 notice are not affected by this notice.

In a followup notice published in the **Federal Register** of August 14, 1974 (39 FR 29210), FDA reevaluated the drug products as less-than-effective (probably effective) as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculo-skeletal conditions. The notice stated that the mode of action of chlorzoxazone has not been clearly identified, but may be related to its sedative properties and that it does not directly relax tense skeletal muscles in humans. Although the chlorzoxazone component was considered effective, the combination products were regarded as only probably effective in the absence of adequate and well-controlled studies showing that they fulfill the requirements of the combination drug policy (21 CFR 300.50).

Responding to the August 14, 1974 notice, McNeil submitted the following for Parafon Forte: (1) A 14-investigator multi-clinic study, (2) a four-investigator multi-clinic study, (3) an eight-investigator multi-clinic study, (4) five additional studies comparing Parafon Forte with other drugs, and (5) five additional studies comparing Parafon Forte with its components, These are discussed below.

Under 21 CFR 300.50, in order to show the contribution of each ingredient to the combination, Parafon Forte should be superior to chlorzoxazone and not worse than acetaminophen alone for the relief of pain; and it should be superior to acetaminophen and not worse than chlorzoxazone for the relief of spasm.

1. *Fourteen-investigator, multi-clinic study.* This study involving 14 investigators was intended to compare Parafon Forte, Paraflex (chlorzoxazone), and placebo for adjunctive treatment of lower back pain related to spasm. The treatment period was to be 5 to 10 days. Concomitant physical therapy was allowed. Patients' records were to be forwarded to the sponsor at the midpoint and at the end of the investigator's study. Physician blinding was to be carried out by having a disinterested third party remove identifying labels from each bottle and seal the labels in an envelope.

Two interim pooled analyses were made by McNeil. The first utilized only four investigators; the second utilized all 14 investigators. In the second analysis the results of the comparison of Parafon Forte and Paraflex are generally negative, with statistically significant results for only 1 of 15 comparisons—the day 4 global evaluation. After the study was complete a pooled analysis of four investigators was made by McNeil. This analysis was reanalysed by McNeil after FDA disqualified one of the four investigators. (See 21 CFR 312.1(c)). Thus, the results of only three out of 13 investigators were evaluated. The analysis measured response to medication for spasm and for pain, reduction in severity of combined symptoms and global evaluation for Parafon Forte and Paraflex at days 2, 4, and the final day. According to the sponsor, statistically significant results favored Parafon Forte over Paraflex for pain relief at day 2 ($p=0.02$) and the final day ($p=0.05$), for spasm relief at day 4 ($p=0.02$) and the final day ($p=0.01$), for combined symptoms at day 4 ($p=0.01$), and for global evaluation at days 2, 4, and the final day ($p<0.001$).

However, the statistical analysis that favors Parafon Forte over Paraflex is based on selection of some data and rejection of other data after the studies were completed, not in accordance with any prior plan. 21 CFR 314.111(a)(5)(ii)(*a*)(*5*). Given that the outcome of any analysis was known to the analyst who carried it out, it is essential that the sponsor show how bias on the part of the analyst was avoided. Moreover, there must be very powerful reasons for dropping any investigator, after the fact, from a multi-center investigation.

There is also reason for concern that there was analyst and investigator bias prior to completion of the study. As was required by the protocol, at the midpoint of the Miller study, which was planned to consist of 60 patients, the records of the 30 patients then in the group were evaluated by the sponsor and found to show that Paraflex was superior to Parafon Forte in global evaluation at all three time points. This study was terminated early, after a total of 41 patients had been treated, and the data from the study not only were never used in the sponsor's analysis, but were never even descriptively summarized. In contrast, investigator Walker, who showed Parafon Forte superior to Paraflex at the time of interim analysis, extended an already completed 30-patient study and finished with 61 patients in his investigation. The sponsor must explain how such apparently disparage treatment of the investigators does not introduce bias with the outcome. In the absence of such explanation, results from this multi-clinic study, no matter how pooled, cannot be considered acceptable.

The sponsor stated that the subgroup of three investigators for the final analysis was selected because each investigator had a sufficient number of patients to allow for individual analysis. In fact however, this is not a sufficient explanation, as several other investigators, such as Chambers, Cullen, and Gingrich had nearly as many. Moreover, the study was planned as a multi-center trial with different numbers of patients per investigator and the expected numbers were in general nearly achieved. To drop the lower number centers belatedly is unjustified, again, with the data in hand the methods used to avoid bias in such selection must be specified. 21 CFR 314.111(a)(5)(ii)(*a*)(*5*).

Two of the investigators included in these analyses present unexplained contradictions in reported status and deviations from the original study plans. Carlson was reported to have finished his study with a sample size of 20 at the time of the interim analysis. In the final analysis Carlson reported results for 51 patients, thus presenting 31 unanticipated patient records. As noted earlier, Walker, who saw 28 patients before the interim analysis, with an anticipated sample size of 30, extended his study and finished with a total of 61 patients. In both cases, the circumstances that led to extensions of some investigators after an interim analysis requires explanation. The analysis of the subset of investigators provides further reasons for concern about the introduction of analyst bias.

In the final analysis, since the protocol specified a treatment period of 5 to 10 days, the sponsor excluded 22

patients who terminated treatment after 4 days. This seems to be an extreme measure for correction of this protocol violation, as the data were analyzed for days 2, 4, and the final day. Termination after day 4 cannot influence the day 2 or day 4 response. In fact, the decision to terminate may be a function of day 4 response, which should not be ignored even when it is the last observation. Twenty one of the 22 patients excluded were investigator Carlson's patients. Noting again that the exclusions were made only after the data had been analyzed and reanalyzed, it must be recognized that when the three investigators, Vernon, Walker, and Carlson, were evaluated separately, Carlson was the only investigator with no statistically significant differences in pairwise comparisons of Parafon Forte and Paraflex. The above exclusion eliminates more than one-third of Carlson's patients from the pooled analysis, diminishing Carlson's contribution to the pooled results.

2. *Four-investigator, multi-clinic study.* This study involved four investigators in a comparison of Parafon Forte, Paraflex, and acetaminophen for treatment of pain and/or spasm of the lower back. The treatment period was to be 5 to 7 days. Concomitant physical therapy was not allowed. The Paraflex tablets used contained 375 mg of chlorzoxazone instead of 250 mg as in the first study. The rest of the procedures were the same as in the first study.

Four analyses of the data were submitted to FDA. The first was a combined analysis from three investigators, one of whom FDA later disqualified. (See 21 CFR 312.1(c)). The second consisted of separate analyses of the four investigators, and the third was an analysis of the data from two investigators, including the one later disqualified. The last was a pooling of the data from the three remaining investigators, Vernon, Walker, and Cullen. This analysis measuring response to medication was evaluated in terms of pain, spasm, combined symptoms, and global evaluation on days 2, 4, and the final day. One-sided p-values favoring Parafon Forte were reported for pain at day 4 ($p=0.03$), combined symptoms at days 2 and 4 (both $p=0.02$), and global evaluation at days 2 and 4 ($p=0.01$ and 0.05 respectively). As with the previous study, none of the sponsor's statistical results favoring Parafon Forte over Paraflex can be accepted as a basis for concluding that this study demonstrates the contribution of acetaminophen to the combination of chlorzoxazone and acetaminophen. A number of points concerning study design, study implementation, and data handling make the results exploratory and conjectural rather than confirmatory and conclusive.

In the fourth analysis, only 43 of the 66 patients who participated in the Walker study were included, making the fourth analysis an interim analysis performed almost 10 years after the study was completed. The reason for such an incomplete analysis requires explanation, particulary with respect to showing how analysis bias was avoided in selecting which patients would be included. Equally important, proper analysis of the data submitted shows that results to do not favor Parafon Forte. In the sponsor analysis the only analysis adjusted for initial spasm severity was the analysis of the effects of treatment on spasm severity. FDA has reanalyzed the data, including all of Walker's patients. The analysis indicates that initial spasm severity was a determining feature for both pain relief and global evaluation. When the analysis is adjusted for both the initial pain and spasm severities, there is no statistically significant difference between Parafon Forte and Paraflex in any of the efficacy variables. In addition, the FDA analysis indicates that there were significant treatment by investigator interactions in most of the variables analyzed. Thus, results of the three investigators should be analyzed separately, as was done in the sponsor's second and third analyses.

As in the first study, since a third party removed and stored the identifying labels from each bottle of medication used, an opportunity existed for physician unblinding which could not be effectively monitored or controlled.

Because the first analysis includes an investigator who was disqualified by FDA, it cannot be used to support the sponsor's claim.

In the second and third analyses only Vernon and the disqualified investigator are reported to have provided results showing that Parafon Forte was superior to Paraflex. Vernon, however, was unable to replicate these results in the 8-investigator study discussed below, which used a smaller Paraflex dose and a larger number of patients. Since he could not replicate the results of his study despite changes in design which should have made a result favoring Parafon Forte more probable, the present study presents no basis for a conclusion that Parafon Forte is superior to Paraflex.

3. *Eight-investigator, multi-clinic study.* In this comparison of Parafon Forte, Paraflex, acetaminophen, and placebo for treatment of pain and/or spasm of the lower back, eight investigators were involved, two of whom were later disqualified by FDA. (See 21 CFR 312.1(c).) The study was double-blind, radomized, of parallel design, and all investigators used similar protocols. It was designed to meet the requirements of the combination drug policy (21 CFR 300.50) by demonstrating that each component of Parafon Forte contributes to the overall therapeutic effect claimed for the drug. The treatment period was to be no more than 7 days. Concomitant physical therapy was not allowed. Patients' records were to be forwarded to the sponsor at the midpoint and at the end of the study. Physician blinding was carried out by using tear-off sealed labels on each bottle. Four of the investigators, three of whom had participated in the previous two studies and one of whom had just completed another study on Parafon Forte, were to enter 100 patients each. The other four investigators, who were not involved in any previous Parafon Forte studies, were to enter 20 to 40 patients each. The specific objectives of the study were to determine the time required for relief of pain, stiffness, and limitation of motion associated with injury, provide comparative data on side effects, and determine the time required for patients to recover from injury and resume pre-injury activity levels. Subjects used in the studies were outpatients 16 years and older with symptoms of moderate to severe pain and/or spasm and limitation of motion associated with the lower back. These patients did not receive other adjunctive treatment during the study or other related medications within 48 hours before admission to the study. They did not have any other ailments that might have had an interfering effect and were not sensitive to any of the medications used in the studies. Patients were randomly assigned to one of the four study treatments and received two capsules four times a day, after meals and at bedtime. Dosage was not titrated to individual patient needs during the study.

Severity of symptoms was recorded at the beginning of the study, at followup office visits on days 2 and 4, and at the end of the study. The symptoms recorded were pain, spasm, tenderness over area of spasm, limitation of motion, and limitation of routine activities. These symptoms were evaluated as follows: (1) Muscle spasm and local pain and tenderness by palpation, rated on a

scale of 1 to 5 (absent to severe); (2) limitation of motion, measured by goniometry and rated as above; and (3) limitations of activities, by historical information, direct observation, or both. The patient report forms provided for recording side effects and for rating overall effects for each evaluation period (global impression).

Four pooled analyses of data were submitted. The first analysis was of all eight investigators, the second was done on seven investigators after one of the investigators was disqualified by FDA, the third analysis was done on the remaining six after another investigator was disqualified. This third analyses was evaluated by FDA and the sponsor then submitted the fourth analysis, consisting of the pooled results of three of the investigators (Cullen, Vernon, and Allen), with the pooled results of three investigators from the first study (Vernon, Walker, and Cullen). The results of the fourth analysis using one-tailed tests found Parafon Forte superior to Paraflex for pain relief at day 2 ($p=0.02$) and the final day ($p=0.05$) and for spasm relief at day 4 ($p=0.004$) and the final day ($p=0.04$).

The results of the first two analyses cannot be used to reach any conclusion because two of the investigators were disqualified by FDA as participants in clinical trials. The third analysis does not demonstrate that acetaminophen contributes to the effect in the combination product, Parafon Forte. (See below.)

The sponsor's fourth analysis is uninterpretable and cannot be used as a basis for demonstrating evidence of effectiveness. 21 CFR 314-111(a)(5)(ii)(*a*)(*5*). The sponsor has pooled the results of 3 investigators from the Fourteen Investigator Multi-Center study, previously discussed, with 3 investigators selected from the 6 investigators of this study who are eligible to be included in the analysis. When analyses are carried out that exclude a large fraction of the available data, it is especially critical for a sponsor to explain how analyst bias was avoided. 21 CFR 314.111(a)(5)(ii)(*a*)(*5*), because it is possible to select data that will prove the desired point. Because in any series of studies, or in two multiclinic studies some clinics will favor one treatment over another simply as a matter of chance, selection of a few clinics out of many could readily produce a favorable result even if the test compound were inert.

The 6-investigator analysis (the firm's third analysis) reported no advantage of Parafon Forte over Paraflex for pain relief. Thus there is no evidence at all that acetaminophen provides its anticipated benefit; i.e., it does not do what it was added to do. It is claimed, however, that Parafon Forte was superior to Paraflex for relief of spasm on "the last day after 4" and the final day. It is of note in this context, that acetaminophen alone was not superior to placebo for relief of spasm, a finding not consistent with the reported effect of acetaminophen on spasm when in combination with chlorzoxazone. While it might be plausible to think acetaminophen could relieve spasm indirectly by relieving pain, acetaminophen did not, alone or added to Paraflex, show an effect on pain in this study. The reported effect on spasm, while not what would be expected, could nonetheless be important if it were a reproducible finding. At the outset it should be noted that the "last day after day 4 group" and the "final day" group are essentially the same, as 90 percent of the patients had their last observation after day 4. There is thus in reality only a single time point, not two, at which the reported result is statistically significant. In addition, the results obtained by different investigators were quite inconsistent. Two of the investigators, Johnson and Lekawa found placebo to be the best treatment for spasm. A third (Klegg), found placebo better than either single drug. Of the 3 investigators who found Parafon Forte and Paraflex effective, one (Vernon) found no difference at all between them.

For the single time period, and for all investigators pooled, Parafon Forte was superior to Paraflex in relief of spasm. This finding has not been replicated and, as observed above, it is not consistent with the rationale for adding acetaminophen to the combination. Moreover, two clinics that found placebo superior to the combination provided a substantial portion of the data showing the combination superior to Paraflex; there is great doubt as to whether 6 clinics with such disparate results can be pooled.

In summary, the three multi-clinic studies described above provide no evidence that there is greater pain relief when acetaminophen is part of the treatment. Each succeeding study was designed to improve the chance of detecting a difference between Parafon Forte and Paraflex. The first study utilized concomitant physical therapy. The second study did not allow concomitant therapy, though it did increase the dose of Paraflex. The third study involved increased sample sizes, a return to the original Paraflex dose, continued proscribing of concomitant therapy, and the participation of four experienced investigators. Despite the progression in study designs, the later studies did not replicate the few favorable results of early studies and produced inconsistent and inconclusive results.

To reach the most favorable analyses of these three studies, the sponsor did not use the results of all investigators but chose particular investigators out of the group. Such post-facto selection raises the possibility of analyst bias and requires detailed explanation of how such bias was avoided. The occasional favorable results must be expected given the multiple studies and multiple end-points within studies. There has been no attempt to correct the statistical analyses for multiple comparisons, a critical correction when multiple measures (pain, spasm and multiple time points) are analyzed. 21 CFR 314.111(a)(5)(ii)(*a*)(*5*).

4. *Five additional studies comparing Parafon Forte with other drugs.* These were double-blind, randomized studies comparing the efficacy of Parafon Forte with Robaxisal, Soma Compound, or Norgesic—drug products used in the relief of acute musculo-skeletal pain. The five studies used the same protocol but were analyzed separately. The Gready and Miller studies and one by Clegg reported Parafon Forte to be more effective than the other muscle relaxants tested, while the Parafon study and the second Clegg study showed no significant difference between the drugs tested. The studies cannot, however, demonstrate the effectiveness of Parafon Forte as a fixed combination because they do not compare Parafon Forte with each of its components and thus cannot demonstrate what contribution, if any, acetaminophen makes to the combination product, a contribution required by 21 CFR 300.50. The other component in Parafon Forte, chlorzoxazone, has already been classified as effective.

5. *Five additional studies comparing Parafon Forte with its components.* The sponsor also submitted information on five additional studies identified as ASMS-1 to ASMS-5.

*ASMS-1 study.* This was discontinued in 1979 due to administrative problems. No conclusions could be derived as an insufficient number of patients were evaluated.

*ASMS-2 study.* This was started in early 1980 and later amended. Only 40 patients have been enrolled in the study and the sponsor has stated that until an adequate number of patients are enrolled no further analysis of the data will be done.

*ASMS–3 study.* This is a double-blind, multi-clinic study comparing Parafon Forte, Paraflex, acetaminophen, and placebo in patients who have moderate to severe pain and tenderness and spasm of acute origin. The protocol stated that the duration of the study is not to exceed 9 months. The protocol called for 27 investigators and 1,316 patients: each investigator was to have 48 patients, 12 on each of the four treatments.

This study began in June 1980. After 11 months only 21 investigators and 138 patients were involved in the study. The most patients enrolled by an investigator is 24 by Cullen; the next highest number is 14 by Herz. Several—Caldwell, Mehlish, Dickinson, and Murray—had as few as two. Hammerman and Williams each had no patients enrolled.

Patients were randomly assigned to one of the four treatment groups and were instructed to take a fixed dosage four times a day throughout the study. Patients were evaluated by the investigator on day 1 before taking the medication and then on the next four days. If the fifth day fell on a weekend, that evaluation was to be scheduled on the next most convenient day.

At each visit the patient was evaluated for the following parameters: Degree of pain and tenderness upon palpation, degree of muscle spasm upon palpation, degree of limitation of motion, and degree of interference with normal daily activities. The severity of each of these parameters was to be evaluated by the investigator on a five-point scale: 0=absent, 1=mild, up to 4=severe. At each visit after baseline, both the investigator and patient were to record their evaluation of the global therapeutic response using the following scale: Marked response; moderate response; minimal response; no change; worse. At each visit, the patient was to record an assessment of pain intensity using a 10-centimeter linear pain scale (i.e., Analogue scale). One end of the scale is labeled "no pain" and the other end is labeled "unbearable pain." In addition, using a questionnaire supplied by the investigator, each patient was to record their response to the first dose, and at hourly intervals thereafter was to record evaluation of pain intensity, pain relief, and whether or not the initial pain was at least half relieved. The investigator was to record all adverse reactions which occurred during treatment. There were no significant differences among the four treatment groups in sex, race, and age.

After a statistical analysis on the submitted data, FDA determined that the methods of analysis and evaluation of data were not correctly conducted. 21 CFR 314.111(a)(5)(ii)(*a*)(*5*). This study is of a sequential nature and at each interim analysis the sponsor used statistical methods appropriate only for the fixed sample case—the case where the number of investigators and patients is fixed before the experiment is begun. However, in this study there is no indication of the total (fixed) number of either patients or investigators. The sponsor has made no attempt to adjust the level of significance to accommodate the sequential approach in performing the interim analysis. In general, these adjustments entail having to demonstrate real treatment effects at significance levels lower than in the fixed sample size case for each individual test in order to maintain the significance level at the termination of the study. The sponsor has not specified how many such interim looks at the data are planned. The sponsor has ignored the experimental design in comparing treatments, only the data associated with each paired comparison being used in performing the tests.

The results of the study as reported by the sponsor for the cases evaluated do not show the real level of statistical significance required to distinquish Parafon Forte from placebo or acetaminophen from placebo. This study appears to be of an exploratory nature with investigators terminating the study, low and slow enrollments, and a failure to demonstrate a contribution of the ingredient acetaminophen to the relief of lower back pain.

*ASMS–4 study.* This was started in early 1981 and has only 24 patients who have completed the study. The sponsor maintains that the data will not be analyzed until a sufficiently large sample exists.

*ASMS–5 study.* This was cancelled due to the lack of a suitable model.

The study submitted thus fail to provide substantial evidence that acetaminophen makes a contribution to the combination product Parafon Forte. Accordingly, this combination product is reclassified to lacking substantial evidence of effectiveness for its labeled indication. Inasmuch as no data were submitted for Parafon Tablets, this drug product is also reclassified to lacking substantial evidence of effectiveness.

On the basis of all of the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 300.50 and 314.111(a)(5), that demonstrates the effectiveness of the drug products.

Therefore, notice is given to the holder of the new drug application and to all other interested persons that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the new drug application and all amendments and supplements thereto on the ground that new information before him with respect to the drug products, evaluated together with the evidence available to him when the application was approved, shows there is a lack of substantial evidence that the drug products will have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

In addition to the holder of the new drug application named above, this notice of opportunity for hearing applies to all persons who manufacture or distribute a drug product that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice of opportunity for hearing to determine whether it covers any drug product that the person manufactures or distributes. Such person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of Drug labeling Compliance (address given above).

In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6) e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962 or for any other reason.

In accordance with section 505 of the act (21 U.S.C. 355) and the regulations promulgated under it (21 CFR Parts 310, 314), the applicant and all other persons subject to this notice under 21 CFR 310.6 are hereby given an opportunity for a hearing to show why approval of the new drug application should not be withdrawn and an opportunity to raise,

for administrative determination, all issues relating to the legal status of a drug product named above and of all identical, related or similar drug products.

An applicant or any other person subject to this notice under 21 CFR 310.6 who decides to seek a hearing shall file (1) on or before June 24, 1982, a written notice of appearance and request for hearing, and (2) on or before July 26, 1982, the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of the applicant or any other person subject to this notice under 21 CFR 310.6 to file timely written notice of appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by the person not to make use of the opportunity for a hearing concerning the action proposed with respect to the product and constitutes a waiver of any contentions concerning the legal status of any such drug product. Any such drug product may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations for denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions pursuant to this notice shall be filed in four copies. Such submissions except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

(Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052-1053, as amended (21 U.S.C. 355)), and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.82))

Dated: April 30, 1982.

J. Richard Crout,

*Director, Bureau of Drugs.*

[FR Doc. 82-14147 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

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**[Docket No. 82N-0095; DESI 6514 and 11935]**

## Drugs for Human Use; Drug Efficacy Study Implementation; Revocation of Exemption for Two Oral Prescription Drugs Offered for Relief of Symptoms of Cough, Cold, or Allergy ("Paragraph XIV/Category 15"); Followup Notice and Opportunity for Hearing

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) revokes the temporary exemption for two oral prescription drug products offered for relief of symptoms of cough, cold, or allergy. The exemption has permitted the products to remain on the market beyond the time limit scheduled for implementatin of the Drug Efficacy Study. FDA reclassifies the products to lacking substantial evidence of effectiveness, proposes to withdraw approval of the new drug applications, and offers an opportunity for a hearing on the proposal.

**DATES:** Revocation of exemption effective May 25, 1982. Hearing requests due on or before June 24, 1982.

**ADDRESSES:** Communications in response to this notice should be identified with Docket No. 82N-0095, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Document Center (HFI-35), Rm. 12A-12.

Requests for hearing, supporting data, and other comments: Dockets Management Branch (HFA-305), Rm. 4-62.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD-501), Bureau of Drugs.

**FOR FURTHER INFORMATION CONTACT:** David T. Read, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

**SUPPLEMENTARY INFORMATION:** In notices published in the **Federal Register** (DESI 6514, February 9, 1973 (38 FR 4006), formerly Docket No. FDC-D-537, and DESI 11935, July 27, 1972 (37 FR 15022)), FDA classified the drug products described below as less than effective for their labeled indications. The 1973 notice also offered an opportunity for a hearing on a proposal to withdraw approval of the new drug applications (NDA's).

Subsequently, in a notice published in the **Federal Register** of December 14, 1973 (38 FR 34481), FDA granted a temporary exemption from the time limits established for completing certain phases of the drug efficacy study (DESI) program, for certain oral prescription drugs offered for relief of cough, cold, allergy, and related symptons. That exemption covered the drugs that are the subject of this notice and superseded the earlier February 1973 notice. The exemption was granted because of the close relationship between drugs sold over the counter (OTC)—and thus subject to the ongoing OTC drug review (21 CFR Part 330)—and prescription drugs offered for relief of cough, cold, allergies, and related symptoms. Postponement of final evaluations on the DESI prescription products enabled the agency to consider the recommendations of the OTC drug review panel in addition to any evidence submitted by NDA holders in response to various DESI notices covering relevant products. Those recommendations and a proposed monograph for over-the-counter cold, cough, allergy, bronchodilator, and antiasthmatic (CCABA) drugs were published in the **Federal Register** of September 9, 1976 (41 FR 38312).

This notice revokes the temporary exemption announced in the **Federal Register** of December 14, 1973. It also proposes to withdraw approval of the new drug applications listed below and offers an opportunity for hearing on the proposal. Persons who wish to request a hearing may do so on or before June 24, 1982.

1. NDA 9-319: Ambenyl Expectorant containing codeine sulfate, bromodiphenhydramine hydrochloride, diphenhydramine hydrochloride, ammonium chloride, potassium guaiacolsulfonate, and menthol; Marion

Laboratories, Inc., Pharmaceutical Division, Marion Industrial Park, 10236 Bunker Ridge Rd., Kansas City, MO 64137. (DESI 6514). NDA was previously owned by Parke-Davis, Division of Warner-Lambert Co.

2. NDA 5-914: As it pertains to Pyribenzamine and Ephedrine Tablets containing tripelennamine hydrochloride and 12 mg ephedrine sulfate; Ciba Pharmaceuticals Co., 556 Morris Ave., Summit, NJ 07901 (DESI 11935).

The OTC drug review panel for CCABA drugs reached the following conclusions which are relevant to Ambenyl Expectorant:

1. There is no evidence to support the effectiveness of ammonium chloride as an expectorant. (41 FR 38359)

2. There are no well-controlled studies documenting the effectiveness of potassium guaiacolsulfonate as an expectorant. (41 FR 38367)

3. Combinations containing an antihistamine and an expectorant are irrational because an expectorant promotes the production of secretions whereas the anticholinergic activity of an antihistamine produces an opposite effect. (41 FR 38326 at paragraph II.C.9.e.(3)).

4. The combination of pharmacologic groups represented by the product was not found to be a safe and effective combination. (41 FR 38326 at paragraph II.C.8.).

The OTC drug review panel for CCABA also reached the following conclusion which is relevant to Pyribenzamine and Ephedrine Tablets, which contains 12 mg ephedrine sulfate: No conclusive data were found to support claims of effectiveness of ephedrine sulfate for doses of 8 to 12 mg. (41 FR 38408).

No person has submitted additional data on the drugs listed above. The Director of the Bureau of Drugs concludes that the holder of the NDA has not shown, for each of the products listed above, that each component makes a contribution to the claimed effects and that the dosage of each component is such that the combination is safe and effective for a significant patient population. 21 CFR 300.50. Therefore each of the products is reclassified to lacking substantial evidence of effectiveness.

In addition to the holders of the new drug applications specifically named above, this notice applies to any person who manufactures or distributes a drug product that is not the subject of an approved new drug application and that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. (This notice does not apply to OTC drugs. 21 CFR 310.6(f). It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product that the person manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of Drug Labeling Compliance (address given above).

On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts who are qualified by scientific training and experience, that meets the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5) and 300.50, and demonstrates the effectiveness of the drug products referred to in this notice.

Notice is given to the holders of the new drug applications, and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug applications and all amendments and supplements thereto providing for the drug products referred to in this notice on the ground that new information before him with respect to the drug products, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence that the drug products will have any of the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

This notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act of because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, or for any other reason.

In accordance with section 505 of the act (21 U.S.C. 355) and the regulations promulgated under it (21 CFR Parts 310, 314), the applicants and all other persons who manufacture or distribute a drug product that is identical, related, or similar to a drug product named above (21 CFR 310.6) and not the subject of a new drug application, are hereby given an opportunity for a hearing to show why approval of the new drug applications should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products not the subject of a new drug application.

Any applicant or other person subject to this notice under 21 CFR 310.6 who decides to seek a hearing shall file (1) on or before June 24, 1982, a written notice of appearance and request for hearing, and (2) on or before July 26, 1982, the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of the applicants or any other person subject to this notice under 21 CFR 310.6 to file a timely written notice of appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by the person not to make use of the opportunity for a hearing concerning the action proposed, and a waiver of any contentions concerning the legal status of the relevant drug product. Any such drug product may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug product from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. It if conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions pursuant to this notice are to be filed in four copies. Except for data and information prohibited from pubic disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

(Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053 as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.70 and 5.82))

Dated April 22, 1982.

J. Richard Crout,

*Director, Bureau of Drugs.*

[FR Doc. 82-14144 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

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[Docket No. 81N-0391; DESI 6514]

## Drugs for Human Use; Drug Efficacy Study Implementation; Revocation of Exemption for Certain Oral Prescription Drugs Offered for Relief of Symptoms of Cough, Cold, or Allergy ("Paragraph XIV/Category 15"); Followup Notice and Opportunity for Hearing.

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) revokes the temporary exemption for three oral prescription drug products offered for relief of symptoms of cough, cold, or allergy. The exemption has permitted the products to remain on the market beyond the time limit scheduled for implementation of Drug Efficacy Study. FDA reclassifies the products to lacking substantial evcidence of effectiveness, proposes to withdraw approval of the new drug applications, and offers an opportunity for a hearing on the proposal. These products are labeled as antitussives.

**DATE:** Revocation of exemption effective May 25, 1982. Hearing requests due on the before June 24, 1982.

**ADDRESSES:** Communications in response to this notice should be identified with Docket No. 81N-0391, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD-501), Bureau of Drugs.

Requests for the report of the National Academy fo Sciences-National Research Council: Public Records and Document Center (HFI-35), Rm. 12A-12.

Requests for hearing, supporting data, and other comments: Dockets Management Branch (HFA-305), Rm. 4-62.

**FOR FURTHER INFORMATION CONTACT:** David T. Read, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fisher Lane, Rockville, MD 20857, 301-443-3650.

**SUPPLEMENTARY INFORMATION:** In a notice (formerly Docket No. FDC-D-537) published in the **Federal Register** of February 9, 1973 (38 FR 4006), FDA classified the drug products described below as lacking substantial evidence of effectiveness for their labeled indications. The notice also offered an opportunity for a hearing on the proposal to withdraw approval of the new drug application (NDA) for each product.

Subsequently, in a notice published in the **Federal Register** of December 14, 1973 (38 FR 34481), FDA granted a temporary exemption from the time limits established for completing certain phases of the drug efficacy study (DESI) program, for certain oral prescription drugs offered for relief of cough, cold, allergy, and related symptoms. That exemption covered the drugs that are the subject of this notice and superseded the February 1973 notice. The exemption was granted because of the close relationship between drugs sold over the counter (OTC)—and thus subject to the ongoing OTC drug review (21 CFR Part 330)—and prescription drugs offered for relief of cough, cold, allergies, and related symptoms. Postponement of final evaluations on the DESI prescription products enabled the agency to consider the recommendations of the OTC review panel in addition to any evidence submitted by NDA holders in response to various DESI notice covering relevant products. Those recommendations and a proposed monograph for over-the-counter cold, cough, allergy, bronchodilator, and antiasthmatic (CCABA) drugs were published in the **Federal Register** of September 9, 1976 (41 FR 38312).

The OTC reached the following conclusions which are relevant to Omni-Tuss Suspension:

1. Combinations containing an antihistamine and an expectorant are irrational because an expectorant promotes the production of secretions whereas the anticholinergic activity of an antihistamine produces an opposite effect. (41 FR 38326 at paragraph II.C.9.e.(3)). Omni-Tuss Suspension contains the antihistamines phenyltoloxamine and chlorpheniramine maleate, and the expectorant guaiacol carbonate.

2. The combination of an antihistamine, an expectorant, an antitussive, and a bronchodilator was not found to be a safe and effective combination. (41 FR 38326 at paragraph II.C.8.).

No person has submitted additional data on the three drugs listed below. The Director of the Bureau of Drugs concludes that the holder of the new drug applications has not shown, for each of the products listed below, that each component makes a contribution to the claimed effects and that the dosage of each component is such that the combination is safe and effective for a significant patient population 21 CFR 300.50. Therefore each of the products is reclassified to lacking substantial evidence of effectiveness.

This notice revokes the temporary exemption announced in the **Federal Register** of December 14, 1973. It also proposes to withdraw approval of the new drug applications listed below, and offers an opportunity for hearing on the proposal. Persons who wish to request a hearing may do so on or before June 24, 1982.

1. NDA 10-768: Tussionex Tablets and Suspension, each containing dihydrocodeinone and phenyltoloxamine dihydrogen sulfate (both as cation exchange resin complexes of sulfonated polystyrene); Pennwalt Corporation, Pharmaceutical Division, 755 Jefferson Rd., Rochester, NY 14623.

2. NDA 12-666: Omni-Tuss Suspension, containing codeine sulfate, phenyltoloxamine dihydrogen sulfate, chlorpheniramine maleate, ephedrine sulfate (all as cation exchange resin complexes of sulfonated polystyrene), and guaiacol carbonate; Pennwalt Corp.

In addition to the holder of the new drug applications specifically named above, this notice applies to any person who manufactures or distributes a drug product that is not the subject of an approved new drug application and that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. (This notice does not apply to OTC drugs. 21 CFR 310.6(f).) It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product that the person manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division

of Drug Labeling Compliance (address given above).

On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts who are qualified by scientific training and experience, that meets the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), 21 CFR 314.111(a)(5), and 21 CFR 300.50 and demonstrates the effectiveness of the drug products referred to in this notice.

Notice is given to the holder of the new drug applications, and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)], withdrawing approval of the new drug applications and all amendments and supplements thereto providing for the drug products referred to in this notice on the ground that new information before him with respect to the drug products, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence that the drug products will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

This notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 210(p) of the act or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, or for any other reason.

In accordance with section 505 of the act (21 U.S.C. 355) and the regulations promulgated under it (21 CFR Parts 310, 314), the applicant and all other persons who manufacture or distribute a drug product that is identical, related, or similar to a drug product named above (21 CFR 310.6) and not the subject of a new drug application, are hereby given an opportunity for a hearing to show why approval of the new drug applications should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products not the subject of a new drug application.

The applicant or other person subject to this notice under 21 CFR 310.6 who decides to seek a hearing shall file (1) on or before June 24, 1982, a written notice of appearance and request for hearing, and (2) on or before July 26, 1982, the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of the applicant or any other person subject to this notice under 21 CFR 310.6 to file a timely written notice of appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by the person not to make use of the opportunity for a hearing concerning the action proposed, and a waiver of any contentions concerning the legal status of the relevant drug product. Any such drug product may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug product from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions pursuant to this notice are to be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

(Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.70 and 5.82))

Dated: February 9, 1982.

**J. Richard Crout,**

*Director, Bureau of Drugs.*

[FR Doc. 82-14146 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

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**[Docket No. 79N-0459]**

## Erythromycin Estolate Revised Labeling

**AGENCY:** Food and Drug Administration (FDA).

**ACTION:** Notice.

**SUMMARY:** In a document published elsewhere in this issue of the Federal Register, The Commissioner of Food and Drugs announced his conclusion on the safety of erythromycin estolate tablets and capsules. Among other findings, the Commissioner concluded that the deletion of the statement "further, the propionyl ester contributes to the activity of the drug through additional hydrolysis to the base at the bacterial cellular level" from the labeling of all dosage forms is warranted.

**DATES:** Supplements to approve antibiotic forms 5 and 6 shall be submitted on or before August 23, 1982. Revised labeling to be used on or before September 22, 1982.

**ADDRESSES:** Communications in response to this notice should be directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD. 20857.

Supplements (identify with the approved antibiotic form 5 and 6 number): John J. Curtis, Division of Anti-infective Drug Products (HFD–140), 301–443–6797.

Requests for opinion of the applicability of this notice to a specific products: Division of Drug Labeling Compliance (HFD–310), Bureau of Drugs.

**FOR FURTHER INFORMATION CONTACT:** Don Leggett,Bureau of Drugs (HFD–32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3650.

**SUPPLEMENTARY INFORMATION:** On December 4, 1979 (44 FR 69670), the Director of the Bureau of Drugs proposed to revoke provisions for certication of erythromycin estolate tablets and capsules based on new data which suggested that, compared with other erythromycins, there was no greater benefit to offset the estolate's relatively greater risk of hepatoxicity. A

public hearing on the safety of erythromycin estolate was held before the Ad Hoc Advisory Committee on Erythromycin Estolate (the Committee) on April 16 and 17, 1981. Data were presented by Eli Lilly (the major manufacturer of erythromycin estolate), Health Research Group, 10 individuals, and the Bureau of Drugs.

The Committee recommended deletion from the labeling of all dosage forms the wording, "further, the propional ester contributes to the activity of the drug through additional hydrolysis to the base at the bacterial cell level." The Commissioner agrees that no data were presented demonstrating that the proponyl ester is hydrolyzed at the bacterial cell level.

This labeling revision is based on a review of the data submitted to the Committee. A comprehensive discussion of this review is contained in a notice published elsewhere in this issue entitled "Erythromycin Estolate: Withdrawal of Proposal to Revoke Provisions for Certification of Tablets and Capsules; Response to Petition; Labeling."

Present holders of approved applications are:

1. 61-896; Eq 500 mg base tablets, Dista Products Co., Division of Eli Lilly & Co., P.O. Box 1407, Indianapolis, IN 46206.
2. 62-897; Eq 125 mg and Eq 250 mg base capsules, Dista Products Co.
3. 62-893; Eq 125 mg base/5 mL powder for reconstitution, oral; Dista Products Co.
4. 62-894; Eq 100 mg base/mL drops, oral; Eq 125 mg base/5 mL suspension, oral; Eq. 250 mg base/5 mL suspension, oral; Dista Products, Co.
5. 62-895; Eq 125 mg base and Eq 250 mg base chewable tablet, Dista Products Co.
6. 62-087; Eq 250 mg base capsules, Danbury Pharmacal, Inc., 131 West Street, Danbury, CT 06810
7. 62-162; Eq 125 mg and 250 mg base capsules, Barr Laboratories, Inc., 265 Livingston St., Northvale, NJ 07647.
8. 62-237; Eq 250 mg base capsules, Zenith Laboratories, 140 LeGrand Ave., Northvale, NJ 07647.

These holders of approved antibiotic forms 5 and 6 shall submit supplements providing for the deletion of the sentence specified above on or before August 23, 1982. The revised labeling shall be put into use by September 22, 1982 for erythromycin estolate drug products intially introduced or initially delivered for introduction into interstate commerce. The revised labeling may be used without advance approval by the Food and Drug Administration.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 201(n), 502, 507, 52 Stat. 1041, 1050-1051 as amended, 59 Stat. 463 as amended, (21 U.S.C. 321(n), 352, 357)) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)).

Dated: May 18, 1982.

**Arthur Hull Hayes, Jr.,**

*Commissioner of Food and Drugs.*

[FR Doc 82-14163 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

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**[Docket No. 82M-0142]**

## CooperVision, Inc., Medicornea Division; Premarket Approval of J-Loop Planar (Model B-13F) and J-Loop Angular (Model B-1H) Posterior Chamber Lenses

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing its approval of the application for premarket approval under the Medical Device Amendments of 1976 of the J-loop Planar (Model B-13F) and J-loop Angular (Model B-1H) Posterior Chamber Lenses sponsored by CooperVision, Inc., Medicornea Division, Seattle, WA. After reviewing the recommendation of the Ophthalmic Device Section of the Opthalmic; Ear, Nose, and Throat; and Dental Devices Panel, FDA notified the sponsor that the application was approved because these posterior chamber intraocular lenses had been shown to be safe and effective for use as recommended in the submitted labeling.

**DATE:** Petitions for administrative review by June 24, 1982.

**ADDRESS:** Requests for copies of the summary of safety and effectiveness data and petitions for administrative review may be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Charles Kyper, Bureau of Medical Devices (HFK-402), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7445.

**SUPPLEMENTARY INFORMATION:** On July 8, 1981, CooperVision, Inc., Medicornea Division, Seattle, WA, submitted to FDA an application for premarket approval of the J-loop Planar (Model B-13F) and J-loop Angular (Model B-1H) Posterior Chamber Lenses. The application was reviewed by the Ophthalmic Device Section of the Ophthalmic; Ear, Nose, and Throat; and Dental Devices Panel, an FDA advisory committee, which recommended approval of the application for the use of these intraocular lenses. On April 23, 1982, FDA approved the application by a letter to the sponsor from the Acting Director of the Bureau of Medical Devices.

A summary of the safety and effectiveness data on which FDA's approval is based is on file in the Dockets Management Branch (address above) and is available upon request from that office. A copy of all approved final labeling is available for public inspection at the Bureau of Medical Devices. Contact Charles Kyper (HFK-402), address above. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

### Opportunity for Administrative Review

Section 515(d)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition under section 515(g) of the act (21 U.S.C. 360e(g)) for administrative review of FDA's decision to approve this application. A petitioner may request either a formal hearing under Part 12 (21 CFR Part 12) of FDA's administrative practices and procedures regulations or a review of the application and of FDA's action by an independent advisory committee of expects. A petition is to be in the form of a petition for reconsideration of FDA action under § 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the Federal Register. If FDA grants the petition, the notice will state the issue to be reviewed, the form of review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before June 24, 1982, file with the Dockets Management Branch (address above), four copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: May 17, 1982.

William F. Randolph,

*Acting Associate Commissioner for Regulatory Affairs.*

[FR Doc. 82-14020 Filed 5-19-82; 10:32 am]

BILLING CODE 4160-01-M

[Docket No. 81N-0396; DESI 6514]

## Drugs for Human Use; Drug Efficacy Study Implementation; Revocation of Exemption for Three Prescription Expectorants ("Paragraph XIV/ Category 15"); Followup Notice and Opportunity for Hearing

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) revokes the temporary exemption for three oral prescription drug products offered for relief of symptoms of cough, cold, or allergy. The exemption has permitted the products to remain on the market beyond the time limit scheduled for implementation of the Drug Efficacy Study. FDA reclassifies the products to lacking substantial evidence of effectiveness, proposes to withdraw approval of the new drug applications (or pertinent parts thereof), and offers an opportunity for a hearing on the proposal. The products are expectorants.

**DATES:** Revocation of exemption effective May 25, 1982. Hearing requests due on or before June 24, 1982.

**ADDRESSES:** Communications in response to this notice should be identified with Docket No. 81N-0396, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD-501), Bureau of Drugs.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Document Center (HFI-35), Rm. 12A-12.

Requests for hearing, supporting data, and other comments: Dockets Management Branch (HFA-305), Rm. 4-62.

**FOR FURTHER INFORMATION CONTACT:** David T. Read, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

**SUPPLEMENTARY INFORMATION:** In a notice published in the Federal Register of February 9, 1973 (38 FR 4006), FDA classified the drug products described below as lacking substantial evidence of effectiveness for their labeled indications. The notice also offered an opportunity for a hearing on the proposal to withdraw approval of the new drug application (NDA) for each product.

Subsequently, in a notice published in the Federal Register of December 14, 1973 (38 FR 34481), FDA granted a temporary exemption from the time limits established for completing certain phases of the drug efficacy study (DESI) program, for certain oral prescription drugs offered for relief of cough, cold, allergy, and related symptons. That exemption covered the drugs that are the subject of this notice and superseded the February 1973 notice. The exemption was granted because of the close relationship between drugs sold over the counter (OTC)—and thus subject to the ongoing OTC drug review (21 CFR Part 330)—and prescription drugs offered for relief of cough, cold, allergies, and related symptoms. Postponement of final evaluations on the DESI prescription products enabled the agency to consider the recommendations of the OTC review panel in addition to any evidence submitted by NDA holders in response to various DESI notices covering relevant products. Those recommendations and a proposed monograph for over-the-counter cold, cough, allergy, bronchodilator, and antiasthmatic (CCABA) drugs were published in the Federal Register on September 9, 1976 (41 FR 38312).

The OTC review panel for CCABA drugs reached the following conclusions which are relevant to the products listed below:

1. Combinations containing an antihistamine and an expectorant are irrational because an expectorant promotes the production of secretions whereas the anticholinergic activity of an antihistamine produces an opposite effect (41 FR 38326 at paragraph II.C.9.e.(3)). (All the products listed below contain an antihistamine and an expectorant.)

2. The combinations of pharmacologic groups represented by the three products listed below were not found to be safe and effective combinations. (41 FR 38326 at paragraph II.C.8.).

No person has submitted additional data on the three drugs listed below. The Director of the Bureau of Drugs concludes that the holders of the new drug applications have not shown, for each of the products listed below, that each component makes a contribution to the claimed effects and that the dosage of each component is such that the combination is safe and effective for a significant patient population. 21 CFR 300.50. Therefore each of the products are reclassified to lacking substantial evidence of effectiveness. No conclusion as to the effectiveness of guaifenesin *per se* is made at this time.

This notice revokes the temporary exemption announced in the Federal Register of December 14, 1973. It also proposes to withdraw approval of the new drug applications listed below (or pertinent parts thereof), and offers an opportunity for hearing on the proposal. Persons who wish to request a hearing may do on or before June 24, 1982.

1. NDA 11-694: as it pertains to Dimetane Expectorant, containing brompheniramine maleate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and guaifenesin (formerly glyceryl guaiacolate); A. H. Robins Co. 1407 Cummings Dr., Richmond, VA 23220.

2. NDA 11-694: as it pertains to Dimetane Expectorant-DC, containing codeine phosphate, brompheniramine maleate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and guaifenesin; A. H. Robins Co.

3. NDA 12-575: Actifed-C Expectorant, containing codeine phosphate, triprolidine hydrochloride, pseudoephedrine hydrochloride, and guaifenesin; Burroughs Wellcome Co., 3030 Cornwallis Rd., Research Triangle Park, NC 27709.

In addition to the holders of the new drug applications specifically named above, this notice applies to any person who manufactures or distributes a drug product that is not the subject of an approved new drug application and that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. (This notice does not apply to OTC drugs. 21 CFR 310.6(f).) It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product that the person manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of Drug Labeling Compliance (address given above).

On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts who are qualified by scientific training and experience, that meets the requirements of section 505 of the Federal Food, Drug, and

Cosmetic Act (21 U.S.C. 355), 21 CFR 314.111(a)(5), and 21 CFR 300.50, and demonstrates the effectiveness of the drug products referred to in this notice.

Notice is given to the holders of the new drug applications, and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug applications and all amendments and supplements thereto providing for the drug products referred to in this notice on the ground that new information before him with respect to the drug products, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence that the drug products will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

This notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, or for any other reason.

In accordance with section 505 of the act (21 U.S.C. 355) and the regulations promulgated under it (21 CFR Parts 310, 314), the applicants and all other persons who manufacture or distribute a drug product that is identical, related, or similar to a drug product named above (21 CFR 310.6) and not the subject of a new drug application, are hereby given an opportunity for a hearing to show why approval of the new drug applications should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products not the subject of a new drug application.

An applicant or other person subject to this notice under 21 CFR 310.6 who decides to seek a hearing shall file (1) on or before June 24, 1982, a written notice of appearance and request for hearing, and (2) on or before July 26, 1982, the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of the applicants or any other person subject to this notice under 21 CFR 310.6 to file a timely written notice of appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by the person not to make use of the opportunity for a hearing concerning the action proposed, and a waiver of any contentions concerning the legal status of the relevant drug product. Any such drug product may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug product from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions pursuant to this notice are to be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.70 and 5.82).

Dated: February 9, 1982.

**J. Richard Crout,**

*Director, Bureau of Drugs.*

[FR Doc. 82-14148 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

**[Docket No. 81N-0393; DESI 6514]**

## Drugs for Human Use; Drug Efficacy Study Implementation; Revocation of Exemption for Five Prescription Expectorants ("Paragraph XIV/ Category 15"); Followup Notice Opportunity for Hearing

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) revokes the temporary exemption for five oral presecription drug products offered for relief of symptoms of cough, cold, or allergy. The exemption has permitted the products to remain on the market beyond the time limited scheduled for implementation of the Drug Efficacy Study. FDA reclassifies the products to lacking substantial evidence of effectiveness, proposes to withdraw approval of the new drug applications, and offers an opportunity for a hearing on the proposal. The products are marketed as expectorants.

**DATES:** Revocation of exemption effective May 25, 1982. Hearing requests due on or before June 24, 1982.

**ADDRESSES:** Communications in response to this notice should be identified with Docket No. 81N-0393, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Request for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD-501), Bureau of Drugs.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Document Center (HFI-35), Rm. 12A-12.

Requests for hearing, supporting data, and other comments: Dockets Management Branch (HFA-305, Rm. 4-62.

**FOR FURTHER INFORMATION CONTACT:** David T. Read, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; 301-443-3650.

**SUPPLEMENTARY INFORMATION:** In a notice (formerly Docket No. FDC-D-537) published in the **Federal Register** of February 9, 1973 (38 FR 4006), FDA classified the drug products described below as lacking substantial evidence of effectiveness for their labeled

indications. The notice also offered an opportunity for a hearing on the proposal to withdraw approval of the new drug application (NDA) for each product.

Subsequently, in a notice published in the Federal Register or December 14, 1973 (38 FR 34481), FDA granted a temporary exemption from the time limits established for completing certain phases of the drug efficacy study (DESI) program, for certain oral prescription drugs offered for relief of cough, cold, allergy, and related symptoms. That exemption covered the drugs that are the subject to this notice and superseded the February 1973 notice. The exemption was granted because of the close relationship between drugs sold over the counter (OTC)—and thus subject to the ongoing OTC drug review (21 CFR Part 330)—and prescription drugs offered for relief of cough, cold, allergies, and related symptoms. Postponement of final evaluation on the DESI prescription products enabled the agency to consider the recommendations of the OTC review panel in addition to any evidence submitted by NDA holders in response to various DESI notices covering relevant products. Those recommendations and a proposed monograph for over-the-counter cold, cough, allegy, bronchodilator, and antiasthmatic (CCABA) drugs were published in the Federal Register of September 9, 1976 (41 FR 38312).

The OTC review panel for CCABA drugs reached the following conclusions which are relevant to the products listed below:

1. There is no evidence to support the effectiveness of ipecac fluid extract as an expectorant. (41 FR 38358)

2. There are no well-controlled studies documenting the effectiveness of potassium guaiacolsulfonate as an expectorant. (41 FR 38367)

3. There are no well-controlled studies documenting the effectiveness of sodium citrate as an expectorant. (41 FR 38367)

4. Combinations containing an antihistamine and an expectorant are irrational because an expectorant promotes the production of secretions whereas the anticholinergic activity of an antihistamine produces an opposite effect. (41 FR 38326 at paragraph II.C.9.e.(3)). (All the products listed below contain promethazine hydrochloride, and antihistamine, and components purported to be expectorants.)

5. The combinations of pharmacologic groups represented by the five products listed below were not found to be safe and effective combinations. (41 FR 38326 at paragraph II.C.8.)

No person has submitted additional data on the five drugs listed below. The Director of the Bureau of Drugs concludes that the holder of the NDA has not shown, for each of the products listed below, that each component makes a contribution to the claimed effects and that the dosage of each component is such that the combination is safe and effective for a significant patient population. 21 CFR 300.50. Therefore each of the products is reclassified to lacking substantial evidence of effectiveness.

This notice revokes the temporary exemption announced in the Federal Register of December 14, 1973. It also proposes to withdraw approval of the new drug applications listed below (or pertinent parts thereof), and offers an opportunity for hearing on the proposal. Persons who wish to request a hearing may do so on or before June 24, 1982.

1. NDA 8-306: as it pertains to Phenergan Expectorant with Codeine, containing promethazine hydrochloride, ipacac fluidextract, potassium guaiacolsulfonate, citric acid, sodium citrate, and codeine phosphate; Wyeth Laboratories, Inc., Division of American Home Products Corp., P.O. Box 8299, Philadelphia, PA 19101. (This product and the four following products formerly contained chloroform. Wyeth removed chloroform from all five formulations in 1976. See 21 CFR 310.513.)

2. NDA 8-306: as it pertains to Phenergan VC Expectorant Plain, containing promethazine hydrochloride, ipecac fluidextract, potassium guaiacolsulfonate, citric acid, sodium citrate, and phenylephrine hydrochloride: Wyeth Laboratories, Inc. (This product was incorrectly identified as NDA 8-604 in the February 9, 1973 notice.)

3. NDA 8-306: as it pertains to Phenergan VC Expectorant with Codeine, containing promethazine hydrochloride, ipecac fluidextract, potassium guaiacolsulfonate, citric acid, sodium citrate, and phenylephrine hydrochloride, and codeine phosphate; Wyeth Laboratories, Inc.

4. NDA 8-604: Phenergan Expectorant Plain, containing promethazine hydrochloride, ipecac fluidextract, potassium guaiacolsulfonate, citric acid, and sodium citrate; Wyeth Laboratories, Inc.

5. NDA 11-265: Pediatric Phenergan Expectorant with dextromethorphan, containing promethazine hydrochloride, ipecac fluidextract, potassium guaiacolsulfonate, citric acid, sodium citrate, and dextromethorphan hydrobromide; Wyeth Laboratories, Inc.

In addition to the holder of the new drug applications specifically named above, this notice applies to any person who manufactures or distributes a drug product that is not the subject of an approved new drug application and that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. (This notice does not apply to OTC drugs. 21 CFR 310.6(f).) It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product that the person manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of Drug Labeling Compliance (address given above).

On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts who are qualified by scientific training and experience, that meets the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5) and 300.50, and demonstrates the effectiveness of the drug products referred to in this notice.

Notice is given to the holder of the new drug applications, and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug applications and all amendments and supplements thereto providing for the drug products referred to in this notice on the ground that new information before him with respect to the drug products, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence that the drug products will have any of the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

This notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, in section 201(p) of the act, or under section 107(c) of the Drug

Amendments of 1962, or for any other reason.

In accordance with section 505 of the act (21 U.S.C. 355) and the regulations promulgated under it (21 CFR Parts 310, 314), the applicant and all other persons who manufacture or distribute a drug product that is identical, related, or similar to a drug product named above (21 CFR 310.6) and not the subject of a new drug application, are hereby given an opportunity for a hearing to show why approval of the new drug applications should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products not the subject of a new drug application.

The applicant or other person subject to this notice under 21 CFR 310.6 who decides to seek a hearing shall file (1) on or before June 24, 1982, a written notice of appearance and request for hearing, and (2) on or before July 26, 1982, the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of the applicant or any other person subject to this notice under 21 CFR 310.6 to file a timely written notice of appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by the person not to make use of the opportunity for a hearing concerning the action proposed, and a waiver of any contentions concerning the legal status of the relevant drug product. Any such drug product may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug product from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions pursuant to this notice are to be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053 as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.70 and 5.82).

Dated: February 9, 1982.

**J. Richard Crout,**

*Director, Bureau of Drugs,*

[FR Doc 82-14150 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## Office of the Secretary

### Privacy Act of 1974; Report of a New System of Records

**AGENCY:** Office of the Assistant Secretary for Planning and Evaluation (ASPE) Office of the Secretary (OS), Department of Health and Human Services (DHHS).

**ACTION:** Notification of a New System of Records, HHS/OS/ASPE 09-90-0090.

**SUMMARY:** In accordance with 5 U.S.C. 552a(e)(4), we are issuing public notice of our intent to establish a new system of records: "Recipient Survey of Alternative Approaches to Financing Day Care for AFDC Children". We are proposing also to include two routine uses with the system in accordance with 5 U.S.C. 552a(e)(11). The proposed new system will provide for data on the nature and extent of the effects that Federal subsidy of child care costs have on AFDC recipients and their families. Non-individually identifiable data will be used for analysis by the contractor, the Urban Institute, and sub-contractor, Westat, any agency of government, and any member of the public who wishes to conduct statistical analyses of such data.

We will collect data from seven sites on approximately 300 individuals. The public is invited to submit comments on the routine uses of this system of records on or before June 17, 1982.

**DATE:** We filed a report of a new system of records with the President of the Senate, the Speaker of the House of Representatives, and the Director, Office of Management and Budget (OMB) on May 18, 1982. The proposed routine uses will become effective on the effective date of the system without further notice, unless we receive comments which would result in a contrary determination.

**ADDRESS:** Interested individuals may comment on this system of records and its routine uses by writing to the ASPE Privacy Officer, Department of Health and Human Services, 200 Independence Avenue, S.W., Washington, D.C. 20201. We will make comments received available for public inspection in Room 436G.12 Alcove, Hubert Humphrey Building, at the above address.

**FOR FURTHER INFORMATION CONTACT:** Project Officer, Recipient Survey of Alternative Approaches to Financing Day Care for AFDC Children, Office of the Assistant Secretary for Planning and Evaluation, 200 Independence Avenue, S.W., Room 447F, Washington, D.C. 20201, telephone number (202) 245-2240.

**SUPPLEMENTARY INFORMATION:** The Assistant Secretary for Planning and Evaluation, Department of Health and Human Services, proposes to initiate a new system of records. We are proposing to establish this system of records as part of an overall effort to examine the various approaches to financing child care for AFDC recipients as well as to gain a better understanding of what State policy is, how it is working and what is likely to occur.

The survey of AFDC recipients is one of several steps in the overall project to examine the effects of alternative approaches to financing day care for AFDC children and will include a system of records with personal identifiers. Other methods of collecting data for this project include telephone interviews and in-person surveys of state and local officials and day care providers, and will not constitute a system of records under the Privacy Act.

Local welfare agencies will identify AFDC recipients for participation in the survey. Interviews with recipients agreeing to participate in the survey will be conducted by the sub-contractor, Westat, in recipients' homes. Approximately 300 AFDC recipients receiving child care subsidies will be interviewed.

In order to achieve the purpose of the study, AFDC recipients will be interviewed face-to-face. An interview of this type will determine the extent of the recipients' child care arrangements, and the advantages and disadvantages of each type, especially the way in which child care arrangement interacts

with recipients' employment and/or training. Inquiries will be made into recipients' feelings about the quality of care their child receives; the extent that the program enables the recipient to seek employment, obtain necessary training or maintain a job. The interviewer will also probe into whether the program succeeds or fails to provide necessary care; and the degree to which the program provides incentives or deterrents to continue employment and/or training.

The Privacy Act allows us to disclose information without the consent of the individual for "routine uses," that is, disclosure for purposes which are compatible with the purpose for which we collect information. Accordingly, we are proposing two routine uses.

One is disclosure to a Congressional office from the record of an individual in response to an inquiry from that Congressional office made on behalf of that individual.

Another routine use provides for disclosure to a contractor/sub-contractor of ASPE for performance of research, evaluation and statistical activities in order to accomplish the purposes for which the records are collected.

Also, disclosure may be made to the Department of Justice in the event of litigation where the defendant is the Department of Health and Human Services (HHS), any component of HHS, or any employee of HHS in his or her official capacity; HHS may disclose such records it may deem desirable or necessary to the Department of Justice to enable that Department to present an effective defense, provided such disclosure is compatible with the purpose for which the records were collected.

Survey respondents will be informed that participation is voluntary. The Privacy Act statement will be provided in printed form to all potential respondents so they may have the opportunity to read the statement and provide written consent, prior to any interviews by Westat. At that time, should the respondents have any questions about the purpose of the survey, the interviewer will answer them.

Standard procedures described below will be established by the Urban Institute with respect to the handling and use of personal identifying information which will be gathered in the course of the interview effort.

A project number will be assigned to each client's interview sheet. Thus, becoming his/her identification number. A master list which cross-indexes project numbers with names, addresses and telephone numbers will be kept under lock and key, initially by a field representative from Westat, and then by the Urban Institute's Project Director. The Urban Institute will retain all records for the life of the project with the exception of the master list of recipents' names as described below.

Next, the master list will be given to the Government Project Officer in the Office of the Assistant Secretary for Planning and Evaluation where it will be placed in a locked file. The master list will be maintained so that in the event of a followup study, additional longitudinal data from the same families may be collected. The master list will be destroyed by the Government Project Officer no later than one year after the project ends if no additional research is conducted.

During the period of time that the master list is in the possession of the Urban Institute Project Director it will be accessible only to Westat and the Urban Institute project management staff for the purposes of verifying data or arranging follow-up interviews. Data will then be entered into machine-readable tapes using only project numbers. This procedure will also assure that the respondent's confidentiality is protected. Individual respondents will never be identified in any analyses or reports submitted by the Urban Institute for this project. These data will not be disclosed nor released to any other agency, organization, or individual except under the routine uses of the Privacy Act or as otherwise permitted by law.

This system is neither designed nor intended to be used to measure the behavior of any specific individual with respect to any data that are collected as part of the evaluation.

Since we propose to establish this system in accordance with the requirements of the Privacy Act, we anticipate no adverse effect on the privacy or other personal rights of individuals.

Dated: May 18, 1982.

**Robert J. Rubin,**

*Assistant Secretary for Planning and Evaluation.*

## Notification of New System of Records Required by the Privacy Act of 1974

**09-90-0090**

**SYSTEM NAME:**

Recipient Survey of Alternative Approaches to Financing Day Care for AFDC Children/HHS/OS/ASPE.

**SECURITY CLASSIFICATION:**

None.

**SYSTEM LOCATION:**

The Urban Institute, 2100 M Street, N.W., Washington, D.C. 20037.

**CATEGORIES OF INDIVIDUALS COVERED BY THE SYSTEM:**

The system will include files developed from a sample of approximately 300 recipients of Aid to Families with Dependent Children (AFDC) receiving Federal subsidy for child care at seven sites. The system will contain mostly records of current recipients, however some former recipients may be interviewed.

**CATEGORIES OF RECORDS IN THE SYSTEM:**

The contractor maintains two sets of files. The master list, which contains names, addresses, and telephone numbers of participating AFDC recipients. A project number links this file with the other file. Only the number permits identification of the individual. The written consent of the recipients who agree to participate in the study will be maintained with the master list.

With the exception of the linking number attached, the other file consists of non-individually identifiable information. Non-individually identifiable information being collected includes demographic characteristics, source(s) of income or support, child care history, employment and training experience, length of time in the welfare system, specifics on type or amount of child care, type of provider and nature of child care subsidy.

**AUTHORITY FOR MAINTENANCE OF THE SYSTEM:**

42 U.S.C. 626, 42 U.S.C. 641, and 42 U.S.C. 1397e.

**PURPOSE OF THE SYSTEM OF RECORDS:**

The proposed new system will provide data for the purpose of examining the various approaches to financing child care for AFDC recipients as well as obtaining a better understanding of State policy, how it is working and what is likely to occur. This system will also determine:

1. Types and quality of child care arrangements under different financing approaches;
2. The effect of the type and quality of care on the employment of AFDC recipients; and
3. The relative costs of different State approaches to financing day care.

**ROUTINE USES OF RECORDS MAINTAINED IN THE SYSTEM, INCLUDING CATEGORIES OF USERS AND THE PURPOSE OF SUCH USES:**

Disclosure may be made to a congressional office from the record of an individual in response to an inquiry

from the congressional office made on behalf of that individual.

In addition, disclosure may be made to a contractor/sub-contractor in order to perform the duties compatible with, and necessary for the purpose for which the data were collected. The contractor shall be required to maintain Privacy Act safeguards with respect to those records.

Also, disclosure may be made to the Department of Justice in the event of litigation where the defendant is the Department of Health and Human Services (HHS), any component of HHS, or any employee of HHS in his or her official capacity; HHS may disclose such records it may deem desirable or necessary to the Department of Justice to enable that Department to present an effective defense, provided such disclosure is compatible with the purpose for which the records were collected.

**STORAGE:**

Magnetic tape and disk, paper records. A non-automated master list of names will be stored in a locked file. Automated recipient records containing no personal identifiers will be stored on magnetic tape and disk.

**RETRIEVABILITY:**

The matching of data in recipient records with personal identifiers will only be authorized by Westat and the Urban Institute project management staff for the following reasons:

1. Verification of data; and
2. At the request of a recipient in the sample.

**SAFEGUARDS:**

(Access controls) Access to the non-automated master list will be limited to Westat and the Urban Institute project management staff for the two reasons cited above, and only during the data collection phase of the project as described in the Retention and Disposal Section below.

**RETENTION AND DISPOSAL:**

During the collection phase of this project, the master list of names and project numbers will be stored under lock and key by the sub-contractor, Westat. Westat, upon completion of the interview and any necessary follow-up will then submit the master list of names to the Urban Institute Project Director for locked storage. The Project Director will maintain the master list in locked files throughout the collection phase. Upon conclusion of the collection phase the Project Director will give the master list of names and project numbers to the Government Project Officer, where they will be placed in a locked file. In the event of a follow-up study these same families, may be contacted. The names will be destroyed by the Government Project Officer no later than one year after the project ends if no subsequent research is conducted.

**SYSTEM MANAGER(S) AND ADDRESS:**

Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, 200 Independence Avenue, S.W., Room 457F, H.H.H. Building, Washington, D.C. 20201.

**NOTIFICATION PROCEDURES:**

Inquiries related to information in this system should be directed to the Government Project Officer, at the address below, and should include full name and current address. Simultaneously, with requesting notification of inclusion in the system of records, the individual may request record access as described in the Record Access Procedures Section.

Project Officer, "Recipient Survey to Examine the Effects of Alternative Approaches to Financing Day Care for AFDC Children"

Office of the Assistant Secretary for Planning and Evaluation, Room 447F, U.S. Department of Health and Human Services, 200 Independence Avenue, S.W., Washington, D.C. 20201.

**RECORD ACCESS PROCEDURES:**

Individuals who, through the notification procedures set forth above have established that the system of records contains information pertaining to them may request access to these records by writing the Government Project Officer at the address given above. The Government Project Officer will notify the individual as to the place and time for access to the record(s). If the requester prefers, and the information requested is not too voluminous, the material may be mailed.

**CONTESTING RECORD PROCEDURES:**

Contact the Government Project Officer at the address given above, give full name and address, specify the information being contested, the rationale for the challenge and supply the information proposed for substitution.

**RECORD SOURCE CATEGORIES:**

Information will be obtained from face-to-face interviews, client information systems and recipient case files.

**SYSTEM EXEMPTED FROM CERTAIN PROVISIONS OF THE ACT:**

None.

[FR Doc. 82-14132 Filed 5-24-82; 8:45 am]
BILLING CODE 4150-04-M

## DEPARTMENT OF THE INTERIOR

## Bureau of Land Management

## Off-Road Vehicle Designation Decision

**AGENCY:** Casper District, Bureau of Land Management, Interior.

**ACTION:** Notice of Off-Road Vehicle Designation Decisions.

**SUMMARY:** The Casper District, Bureau of Land Management has completed decisions to designate 1,153,385 acres of public land in Natrona County, Wyoming as open, limited, or closed to off-road vehicle use. Designations are a result of land use planning decisions made in the 1980 Natrona Management Framework Plan. During planning, comments were received on various areas proposed for designation. In addition, information letters inviting comment were sent to 250 interested individuals and organizations.

The effect of the designation is to limit off-road vehicle use on most public lands to existing roads and vehicle routes. However, most public lands are open to oversnow vehicle use. Use on a few areas is limited to designated roads and vehicle routes and two areas are closed to all motorized vehicles.

**DATES:** The decisions will become final June 24, 1982.

**FOR FURTHER INFORMATION CONTACT:**

Jim Melton, Area Manager, Platte River Resources Area, 951 Rancho Road, Casper, Wyoming 82601, (307) 261-5556

Paul Arrasmith, District Manager, Casper District Office, 951 Rancho Road, Casper, Wyoming 82601, (307) 261-5101.

**SUPPLEMENTARY INFORMATION:** The authority for this decision is derived from Executive Orders 11644 and 11989 and regulations contained in 43 CFR 8340.

Specific area designation are as follows:

*Open Designation*

No areas were identified for open designation.

*Limited Designation*

1. On the majority of public lands (1,087,597 acres) use of off-road vehicles, except oversnow vehicles, is limited to existing roads and vehicle routes. The

lands will be open to oversnow vehicles. Existing roads and vehicle routes are routes constructed, or created by the frequent passage of motor vehicles, prior to October 1, 1980, and currently receiving regular and continuous use. Temporary excursions leaving existing vehicular routes are permitted only to accomplish *necessary tasks* and only if such travel does not result in resource damage such as erosion, water pollution, ruts or other long-term signs of vehicle use. Necessary tasks are work requiring the use of a motor vehicle.

Random or unnecessary travel from existing vehicle routes is not allowed. Creation of new routes, or extension or widening of existing routes, is not allowed without prior written approval by the district manager.

This designation was determined to be appropriate for a majority of the public lands because it accommodates access needs while providing for resource protection.

2. Off-road vehicle use on the following areas is limited to designated roads and vehicle routes:

A. Sand Dunes (13,560 acres) 10 miles northeast of Casper, Wyoming.

B. Jackson and Little Red Creek Canyon Area (3,890 acres) 10 miles southwest of Casper, Wyoming on the west end of Casper Mountain.

C. North Platte River (2,990 acres) between Alcova and Casper, Wyoming.

D. The Red Wall (32,295 acres) in northern Natrona County.

The Sand Dunes, North Platte River and Red Wall are open to oversnow vehicles. In the Jackson and Little Red Creek Canyon Area, oversnow vehicles are also prohibited.

Vehicle travel will be permitted on roads and vehicle routes designated by BLM. Until maps are issued and signs posted, vehicular travel is limited to existing roads and vehicle routes.

3. Off-road vehicle use, including oversnow vehicle use, on two existing recreation management areas is also limited to designated roads and vehicle routes. These areas have been signed.

A. Muddy Mountain Recreation Area (11,370 acres) located 10 miles south of Casper, Wyoming on Muddy Mountain.

B. Goldeneye Wildlife and Recreation Area (733 acres) 20 miles northwest of Casper, Wyoming.

*Closed Designation*

The following 950 acres are closed year long to all motorized vehicles:

1. Eastern portion of the Environmental Education Area on Muddy Mountain (630 acres) approximately 13 miles south of Casper, Wyoming.

2. Oregon Trail wagon ruts along (approximately 320 acres) the Oregon Trail Road, from Casper, Wyoming 45 miles southeast of Pathfinder Reservoir.

Any person(s) having special access needs may apply for a permit to enter an area. Any constructed access will require a right-of-way under 43 CFR 2800.

An environmental assessment describing the impact of these designations was completed and a finding of no significant environmental impact was determined. This document is available for inspection at the office listed above.

**Paul W. Arrasmith,**

*District Manager.*

[FR Doc. 82-14187 Filed 5-24-82; 8:45 am]

BILLING CODE 4310-84-M

## Colorado; Boundary Modification of the Weber Mountain and Menefee Mountain Wilderness Study Areas

This notice serves as an amendment to my previous intensive inventory decision for the Weber Mountain Wilderness Study Area (CO-030-252) and the Menefee Mountain Wilderness Study Area (CO-030-251) as announced by publication in the **Federal Register,** Vol. 45, No. 222, Friday, November 14, 1980 and Vol. 46, No. 2, Monday, January 5, 1981. This notice also serves to announce a protest period on my decision to amend the boundary of both the Weber Mountain and Menefee Mountain Wilderness Study Areas which begins on the date of this announcement and ends June 24, 1982.

The Weber Mountain unit was originally identified as a 6,320 acre Wilderness Study Area (WSA) and the Menefee Mountain unit was identified as a 7,360 acre WSA. A resurvey of the public land along the southeastern boundary of the Weber Mountain WSA by Cadastral Survey (Approved July 31, 1981) defines the public land as approximately one-eighth mile west of the described WSA boundary. In addition, an established irrigation ditch was identified that was not recorded during the Wilderness inventory process. This survey also defines the public land in the southwestern corner of the Menefee Mountain WSA as approximately one-eighth mile west of the described boundary.

It is my decision, therefore, to modify the existing Weber Mountain WSA boundary to parallel the west side of the established irrigation ditch within public lands, and to coincide with the recent survey lines where the public land and private land delineate the boundary. The Weber Mountain WSA would therefore contain 6,200 acres of public lands. In addition, it is my decision to modify the existing Menefee Mountain WSA boundry to coincide with the recent survey lines where the public land and private land delineate the boundary. The Menefee Mountain WSA would therefore contain 7,400 acres of public lands.

Persons wishing to protest my decision announced herein must file a written protest with the Colorado State Director, Colorado State Office, Bureau of Land Management, 1037 20th Street, Denver, Colorado 80202, on or before 4:00 p.m., June 24, 1982. Only those protests received by the Colorado State Office by the time and date specified will be accepted.

The protest must include a clear and concise statement of the reasons for the protest, as well as data to support the reasons stated. The State Director will issue a written decision on any protest which is filed according to the above requirements and will publish a notice in the **Federal Register** of the action taken in response to the protest.

Any person adversely affected by the State Director's decision on a written protest may appeal such decision under the provisions of 43 CFR Part 4.

Information on the Weber Mountain Wilderness Study Area can be obtained by contacting BLM personnel at the following location: Montrose District Office, (303) 249-7791, 2465 South Townsend, P.O. Box 1269, Montrose, Colorado 81402, District Manager: Marlyn V. Jones, Wilderness Specialist: Jon Wesley Sering.

In Denver contact: Colorado State Office, 1037 20th Street, Denver, Colorado 80202; State Wilderness Coordinator: Barry Tollefson, (303) 837-3393.

Dated: May 25, 1982.

**George C. Francis,**

*State Director, Colorado, Bureau of Land Management, Denver, Colorado.*

[FR Doc. 82-13696 Filed 5-24-82; 8:45 am]

BILLING CODE 4310-84-M

## Alaska Outer Continental Shelf; Availability of Final Environmental Impact Statement Regarding Proposed Diapir Field Oil and Gas Lease Sale No. 71

Pursuant to Section 102(2)(C) of the National Environmental Policy Act of 1969, the Bureau of Land Management has prepared a final environmental impact statement relating to a proposed Outer Continental Shelf (OCS) oil and gas lease sale of 372 tracts consisting of approximately 744,000 hectares (1.8

million acres) of submerged Federal lands in the Diapir Field, off the northern coast of Alaska (OCS Sale No. 71).

Single copies of the final environmental impact statement can be obtained from the Office of the Manager, Bureau of Land Management, Alaska Outer Continental Shelf Office, P.O. Box 1159, Anchorage, Alaska 99510, and from the Office of Public Affairs, Bureau of Land Management (130), Washington, D.C. 20240.

Copies of the final environmental impact statement will also be made available for inspection in the following public libraries: Alaska Federation of Natives, 1577 O Street, Suite 304, Anchorage, AK 99501; Anchor Point Public Library, Anchor Point, AK 99556; Department of the Interior Resources Library, 701 "C" Street, Box 36, Anchorage, AK 99513; Cordova Public Library, Box 472, Cordova, AK 99574; Kenai Community Library, Box 157, Kenai, AK 99611; Elim, Learning Center, Elim AK 99739; Haines Public Library, P.O. Box 36, Haines, AK 99827; North Star Borough Library, Fairbanks, AK 99701; University of Alaska, Institute of Social and Economic Research Library, Fairbanks, AK 99801; Homer Public Library, Box 356, Homer, AK 99603; Z. J. Loussac Public Library, 427 F Street, Anchorage, AK 99801; Juneau Memorial Library, 114 W. 4th Street, Juneau, AK 99824; Alaska State Library, Documents Librarian, Pouch G, Juneau, AK 99811; Ketchikan Public Library, 629 Dock Street, Ketchikan, AK 99901; Department of Defense, Army Corps of Engineers Library, P.O. Box 7002, Anchorage, AK 99501; Kodiak Public Library, P.O. Box 985, Kodiak, AK 99615; Metlakatla Extension Center, Metlakatla, AK 99926; Department of Interior, Bureau of Mines Library, AF-F.O. Center, P.O. Box 550, Juneau, AK 99802; Petersburg Extension Center, Box 289, Petersburg, AK 99833; Seldovia Public Library, Drawer D, Seldovia, AK 99663; Seward Community Library, Box 537, Seward, AK 99664; University of Alaska Juneau Library, P.O. Box 1447, Juneau, AK 91447; Sitka Community Library, Box 1090, Sitka, AK 99835; Douglas Public Library, Box 469, Douglas, AK 99824; University of Alaska Anchorage Library, 3211 Providence Drive, Anchorage, AK 99504; University of Alaska Elmer E. Rasumsson Library, Fairbanks, AK 99701; Wrangell Extension Center, Box 651, Wrangell, AK 99929.

**Arnold E. Petty,**

*Acting Associate Director, Bureau of Land Management.*

May 4, 1982.

Approved:

**Bruce Blanchard,**

*Director, Environmental Project Review.*

[FR Doc. 82-14221 Filed 5-24-82; 8:45 am]

BILLING CODE 4310-84-M

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[OR 11304]

## Oregon; Partial Termination of Proposed Withdrawal and Reservation of Lands

*Correction*

In FR Doc. 82-10371 appearing on page 16420 in the issue of Friday, April 16, 1982; in the first column, in the land description under T. 40 S., R. 8 W., the first line of Section 5 should read "Sec. 5, Fractional NE¼NE¼, S½NE¼, and"; first line of Section 15 should read "Sec. 15, NE¼, E½NW¼, S½NE¼, and".

BILLING CODE 1505-01-M

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## Fish and Wildlife Service

## Louisiana; Application

Notice is hereby given that under section 28 of the Mineral Leasing Act of 1920 (30 U.S.C. 185) as amended by Pub. L. 93-153, Cities Service Company has applied for a 6-inch natural gas pipeline right-of-way that will cross the following lands:

T. 13 S. R. 13 W.,
Sec. 1.
T. 13 S. R. 12 W.,
Secs. 1, 2, 3, 4, 5, 6.
T. 13 S. R. 11 W.,
Sec. 6.

This pipeline will convey natural gas across 5.658 miles of the Sabine National Wildlife Refuge, Cameron Parish, Louisiana.

The purpose of this notice is to inform the public that the United States Fish and Wildlife Service will be proceeding with consideration of whether the application should be approved, and if so, under what terms and conditions.

Interested persons desiring to express their views should do so within thirty (30) days and send their name and address to the Regional Director, United States Fish and Wildlife Service, 75 Spring Street, SW., Atlanta, Georgia 30303-3376.

Dated: April 28, 1982.

**James W. Pulliam,**

*Regional Director.*

[FR Doc. 82-14104 Filed 5-24-82; 8:45 am]

BILLING CODE 4310-55-M

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## Minerals Management Service

## Oil and Gas and Sulphur Operations in the Outer Continental Shelf; Chevron U.S.A.

**AGENCY:** Minerals Management Service, Interior.

**ACTION:** Notice of Receipt of a Proposed Development and Production Plan.

**SUMMARY:** Notice is hereby given that Chevron U.S.A. Inc. has submitted a Development and Production Plan describing the activities it proposes to conduct on Lease OCS-G 1241, Block 52, South Timbalier Area, Offshore Louisiana.

The purpose of this Notice is to inform the public, pursuant to Section 25 of the OCS Lands Act Amendments of 1978, that the Minerals Management Service is considering approval of the Plan and that it is available for public review at the Office of the Minerals Manager, Gulf of Mexico OCS Region, Minerals Management Service, 3301 North Causeway Blvd., Room 147, Metairie, Louisiana 70002.

**FOR FURTHER INFORMATION CONTACT:** Minerals Management Service, Public Records, Room 147, Open weekdays 9 a.m. to 3:30 p.m., 3301 North Causeway Blvd., Metairie, Louisiana 70002, Phone (504) 837-4720, Ext. 226.

**SUPPLEMENTARY INFORMATION:** Revised rules governing practices and procedures under which the Minerals Management Service makes information contained in Development and Production Plans available to affected States, executives of affected local governments, and other interested parties became effective December 13, 1979, (44 FR 53685). Those practices and procedures are set out in a revised § 250.34 of Title 30 of the Code of Federal Regulations.

Dated: May 17, 1982.

**Lowell G. Hammons,**

*Minerals Manager, Gulf of Mexico OCS Region.*

[FR Doc. 82-14189 Filed 5-24-82; 8:45 am]

BILLING CODE 4310-31-M

### Oil and Gas and Sulphur Operations in the Outer Continental Shelf; Union Oil Co.

**AGENCY:** Minerals Management Service, Interior.

**ACTION:** Notice of the Receipt of a Proposed Development and Production Plan.

**SUMMARY:** Notice is hereby given that Union Oil Company of California has submitted a Development and Production Plan describing the activities it proposes to conduct on Lease OCS–G 3327, Block 65, Vermilion Area, offshore Louisiana.

The purpose of this Notice is to inform the public, pursuant to Section 25 of the OCS Lands Act Amendments of 1978, that the Minerals Management Service is considering approval of the Plan and that it is available for public review at the Office of the Minerals Management, Gulf of Mexico OCS Region, Minerals Management Service, 3301 North Causeway Blvd., Room 147, Metairie, Louisiana 70002

**FOR FURTHER INFORMATION CONTACT:** Minerals Management Service, Public Records, Room 147, open weekdays 9 a.m. to 3:30 p.m., 3301 North Causeway Blvd., Metairie, Louisiana 70002, Phone (504) 837–4720, Ext. 226.

**SUPPLEMENTARY INFORMATION:** Revised rules governing practices and procedures under which the Minerals Management Service makes information contained in Development and Production Plans available to affected States, executives of affected local governments, and other interested parties became effective December 13, 1979, (44 FR 53685). Those practices and procedures are set out in a revised § 250.34 of Title 30 of the Code of Federal Regulations.

Dated: May 17, 1982.

**Lowell G. Hammons,**

*Minerals Manager, Gulf of Mexico OCS Region.*

[FR Doc. 82–14188 Filed 5–24–82; 8:45 am]

BILLING CODE 4310–31–M

## National Park Service

### Bureau Forms Submitted for Review

The propolsal for the collection of information listed below has been submitted to the Office of Management and Budget for approval under the provisions of the Paperwork Reduction Act (44 U.S.C. Chapter 35). Copies of the proposed information collection requirement and related forms and explanatory material may be obtained by contacting the Bureau's clearance officer at the phone number listed below. Comment and suggestions on the requirement should be made directly to the Bureau clearance officer and the Office of Management and Budget reviewing official, Mr. William T. Adams, at 202–395–7340.

Title: Annual Application.

Bureau Form Number: FHR–8–301 A and B.

Frequency: Annally.

Description of Respondents: State Governments.

Annual Responses: 57.

Annual Burden Hours: 2,280.

Bureau clearance officer: Russell K. Olsen–523⊖5092.

**Russell K. Olsen,**

*Information Collection Clearance Officer.*

May 18, 1982.

[FR Doc. 82–14179 Filed 5–24–82; 8:45 am]

BILLING CODE 4310–70–M

## Office of the Secretary

### Transfer of Alaska Native Claims Appeals Functions

Notice is hereby given that the Secretary of the Interior has issued Order Number 3078 dated April 29, 1982. The Order will consolidate the functions of the Alaska Native Claims Appeal Board into the Interior Board of Land Appeals. The Alaska Native Claims Appeal Board will be abolished. The Order is published in its entirety below.

Additional information regarding the Order may be obtained from the Director, Office of Hearings and Appeals, U.S. Department of the Interior, 4015 Wilson Boulevard, Arlington, Virginia 22203, telephone 703–557–1500.

Dated: May 14, 1982.

**Joseph E. Doddridge,**

*Acting Deputy Assistant Secretary of the Interior.*

April 29, 1982.

Order No. 3078.

Subject: Consolidation of the Alaska Native Claims Appeal Board Functions into the Interior Board of Land Appeals.

Section 1. *Purpose.* This order consolidates the functions of the Alaska Native Claims Appeal Board into the Interior Board of Land Appeals. The purpose of this action is to achieve greater economy in the use of Office of Hearings and Appeals resources in view of the declining number of appeals arising under the Alaska Native Claims Settlement Act, 43 U.S.C. 1601–1628 (1976).

Section 2. *Authority.* This order is issued in accordance with the authority provided by Section 2 of Reorganization Plan No. 3 of 1950 (64 Stat. 1262).

Section 3. *Transfer of Function.* All of the functions and responsibilities delegated to the Alaska Native Claims Appeals Board with respect to appeals arising under the Alaska Native Claims Settlement Act are transferred to the Interior Board of Land Appeals.

Section 4. *Abolishment.* The Alaska Native Claims Appeal Board is abolished.

Section 4. *Implementation.*

(a) The Assistant Secretary—Policy, Budget and Administration is responsible for implementing this order with respect to personnel, property, records and funds.

(b) The Director, Office of Hearings and Appeals, in consultation with the Assistant Secretary—Policy, Budget and Administration, shall make such organizational arrangements for the performance of transferred functions as he deems necessary. In making these arrangements, the Director shall seek to ensure that the rights of parties bringing appeals under the Alaska Native Claims Settlement Act are protected and that no undue delay in consideration of such appeals occurs.

(c) All Alaska Native Claims Settlement Act appeals filed on or after the effective date of this order must be filed in accordance with 43 CFR Part 4, Subpart E.

(d) Changes to Departmental regulations made necessary by this order will be published in the **Federal Register.**

Section 6. *Effective Date.* This order is effective June 30, 1982. The provisions of this order will terminate on December 31, 1982.

Dated: April 29, 1982.

**James G. Watt,**

*Secretary of the Interior.*

[FR Doc. 82–14186 Filed 5–24–82; 8:45 am]

BILLING CODE 4310–10–M

### Information Collections Submitted to OMB for Review

The proposals for the collection of information listed below have been submitted to the Office of Management and Budget for approval under the provisons of the Paperwork Reduction Act (44 U.S.C. Chapter 35). Copies of the proposed information collection requirements and related forms and explanatory material may be obtained by contacting the appropriate Bureau clearance officers at the phone numbers listed below. Comments and suggestions on the requirements should be made directly to the Bureau clearance officer

and the Office of Management and Budget reviewing official, Mr. William T. Adams, at 202–395–7340.

May 19, 1982.

**Vivian A. Keado,**

*Department Clearance Officer, Office of the Secretary.*

Bureau: Office of Surface Mining.
Title: 30 CFR 850, Blaster Certification.
Bureau Form Number: None.
Frequency: Nonrecurring.
Description of Respondents: State Natural Resource Agencies.
Annual Responses: 5,924.
Annual Burden Hours: 311,320.
Bureau Clearance Officer: Darlene Grose 202–343–5447.
Bureau: Geological Survey.
Title: 30 CFR 250.12 Suspension of Operations.
Bureau Form Number: None.
Frequency: Nonrecurring.
Description of Respondents: OCS Federal Mineral Lessees.
Annual Responses: 20.
Annual Burden Hours: 160.
Bureau Clearance Officer: Patrick Cunningham 703–860–7211.
Bureau: Bureau of Land Management.
Title: 43 CFR 3400, Coal Management, Federally Owned Coal.
Bureau Form Number: None.
Frequency: Nonrecurring.
Description of Respondents: Coal Mining Industry, State and Local Government.
Annual Responses: 825.
Annual Burden Hours: 12,400.
Bureau Clearance Officer: Harold Walker, 202–653–8853.
Bureau: Bureau of Land Management.
Title: 43 CFR 3600, Mineral Material Disposal.
Bureau Form Number: 3600–4, 3600–5.
Frequency: Annually.
Description of Respondents: Sand and gravel operators, construction companies, highway departments.
Annual Responses: 6,250.
Annual Burden Hours: 1,250.
Bureau Clearance Officer: Harold Walker 202–653–8853.
Bureau: Bureau of Land Management.
Title: 43 CFR 3833, Recordation of Mining Claims.
Bureau Form Number: None.
Frequency: Annually.
Description of Respondents: Owners of unpatented mining claims, mill sites, and tunnel sites.
Annual Responses: 250,000.
Annual Burden Hours: 20,833.
Bureau Clearance Officer: Harold Walker 202–683–5583.
Bureau: Bureau of Land Management.
Title: 43 CFR 2920, Leases, Permits and Easements Under the Federal Land Policy and Management Act.
Bureau Form Number: 2920–1.
Frequency: Nonrecurring.
Description of Respondents: Any person legally capable of holding lands or interests therein under the laws of the State in which the lands or the interests therein are located.
Annual Responses: 380.
Annual Burden Hours: 3230.
Bureau Clearance Officer: Harold Walker, 202–683–5583.
Bureau: Bureau of Land Management.
Title: Road Use Fees Paid Report.
Bureau Form Number: 5450–8.
Frequency: On occasion.
Description of Respondents: Timber Sale Purchasers.
Annual Responses: 900.
Annual Burden Hours: 270.
Bureau Clearance Officer: Harold Walker 202–683–5583.
Bureau: Bureau of Land Management.
Title: 43 CFR 3200.
Bureau Form Number: 3200–2, 3200–9, 3200–11, 3200–17.
Frequency: Nonrecurring.
Description of Respondents: Individuals, Small Businesses, Large Corporations, State and Local Governments.
Annual Responses: 420.
Annual Burden Hours: 1,449.
Bureau Clearance Officer: Harold Walker, 202–653–8853.

[FR Doc. 82–14185 Filed 5–24–82; 8:45 am]
BILLING CODE 4310–10–M

## Office of Surface Mining

### Bureau Forms Submitted for Review

The proposal for the collection of information listed below has been submitted to the Office of Management and Budget for approval under the provisions of the Paperwork Reduction Act (44 U.S.C. Chapter 35). Copies of the proposed information collection requirement and explanatory material may be obtained by contacting the Bureau's clearance officer at the phone number listed below. Comments and suggestions on the requirement should be made directly to the Bureau clearance officer and the Office of Management and Budget reviewing official, Mr. William T. Adams, at 202–395–7340.

Title: 30 CFR 776 General Requirements for Coal Exploration.
Bureau Form Number: None.
Frequency: On occasion.
Description of Respondents: Coal Mine Operators.
Annual Responses: 2,250.
Annual Burden Hours: 162,500.
Bureau clearance officer: Darlene Grose 202–343–5447.

**Carson W. Culp,**

*Acting Assistant Director, Management and Budget.*

4May 18, 1982.

[FR Doc. 82–14187 Filed 5–24–82; 8:45 am]
BILLING CODE 4310–05–M

### Bureau Forms Submitted for Review

The proposal for the collection of information listed below has been submitted to the Office of Management and Budget for approval under the provisions of the Paperwork Reduction Act (44 U.S.C. Chapter 35). Copies of the proposed information collection requirement and explanatory material may be obtained by contracting the Bureau's clearance officer at the phone number listed below. Comments and suggestions on the requirement should be made directly to the Bureau clearance officer and the Office of Management and Budget reviewing official, Mr. William T. Adams, at 202–395–7340.

Title: 30 CFR 784 Underground Mining Permit Applications—Minimum Requirements for Reclamation and Operation Plan.
Bureau Form Number: None.
Frequency: On occasion.
Description of Respondents: Coal Mine Operators.
Annual Responses: 41,923.
Annual Burden Hours: 791,396.
Bureau clearance officer: Darlene Grose, 202–343–5447.

**Carson W. Culp,**

*Acting Assistant Director, Management and Budget.*

May 18, 1982.

[FR Doc. 82–14180 Filed 5–24–82; 8:45 am]
BILLING CODE 4310–05–M

### Bureau Forms Submitted for Review

The proposal for the collection of information listed below has been submitted to the Office of Management and Budget for approval under the provisions of the Paperwork Reduction Act (44 U.S.C. Chapter 35). Copies of proposed information collection requirement and explanatory material may be obtained by contacting the Bureau's clearance officer at the phone number listed below. Comments and suggestions on the requirement should be made directly to the Bureau clearance officer and the Office of Management and Budget reviewing official, Mr. William T. Adams, at 202–395–7340.

Title: 30 CFR 771 General Requirements for Permits and Permits Applications.

Bureau Form Number: None.

Frequency: Once.

Description of Respondents: Coal Mine Operators.

Annual Responses: 4,843.

Annual Burden Hours: 31,576.

Bureau clearance officer: Darlene Grose 202–343–5447.

**Carson W. Culp,**

*Acting Assistant Director, Management and Budget.*

May 18, 1982.

[FR Doc. 82–14181 Filed 5–24–82; 8:45 am]

BILLING CODE 4310–05–M

## INTERSTATE COMMERCE COMMISSION

### Motor Carriers; Permanent Authority Decisions; Decision-Notice

The following applications, filed on or after February 9, 1981, are governed by Special Rule of the Commission's Rules of Practice, see 49 CFR 1100.251. Special Rule 251 was published in the **Federal Register** on December 31, 1980, at 45 FR 86771. For compliance procedures, refer to the **Federal Register** issue of December 3, 1980, at 45 FR 80109.

Persons wishing to oppose an application must follow the rules under 49 CFR 1100.252. Applications may be protested *only* on the grounds that applicant is not fit, willing, and able to provide the transportation service or to comply with the appropriate statutes and Commission regulations. A copy of any application, including all supporting evidence, can be obtained from applicant's representative upon request and payment to applicant's representative of $10.00.

Amendments to the request for authority are not allowed. Some of the applications may have been modified prior to publication to conform to the Commission's policy of simplifying grants of operating authority.

#### Findings

With the exception of those applications involving duly noted problems (e.g., unresolved common control, fitness, water carrier dual operations, or jurisdictional questions) we find, preliminarily, that each applicant has demonstrated a public need for the proposed operations and that it is fit, willing, and able to perform the services proposed, and to conform to the requirements of Title 49, Subtitle IV, United States Code, and the Commission's regulations. This presumption shall not be deemed to exist where the application is opposed. Except where noted, this decision is neither a major Federal action significantly affecting the quality of the human environment nor a major regulatory action under the Energy Policy and Conservation Act of 1975.

In the absence of legally sufficient opposition in the form of verified statements filed on or before 45 days from date of publication (or, if the application later become unopposed), appropriate authorizing documents will be issued to applicants with regulated operations (except those with duly noted problems) and will remain in full effect only as long as the applicant maintains appropriate compliance. The unopposed applications involving new entrants will be subject to the issuance of an effective notice setting forth the compliance requirements which must be satisfied before the authority will be issued. Once this compliance is met, the authority will be issued.

Within 60 days after publication an applicant may file a verified statement in rebuttal to any statement in opposition.

To the extent that any of the authority granted may duplicate an applicant's other authority, the duplication shall be construed as conferring only a single operating right.

**Note.**—All applications are for authority to operate as a motor common carrier in interstate or foreign commerce over irregular routes, unless noted otherwise. Applications for motor contract carrier authority are those where service is for a named shipper "under contract."

Please direct status inquiries to the Ombudsman's Office, (202) 275–7326.

#### Volume No. OP1–87

Decided: May 12, 1982.

By the Commission, Review Board No. 1, Members Parker Chandler, and Fortier. (Member Parker not participating.)

MC 99680 (Sub-20), filed May 5, 1982. Applicant: NORTH SHORE & CENTRAL ILLINOIS FREIGHT CO., 7701 W. 95th St., Hickory Hills, IL 60457. Representative: James C. Hardman, 33 N. LaSalle St., Chicago, IL 60602; (312) 236–5944. Transporting *general commodities* (except classes A and B explosives, household goods and commodities in bulk), between Uniontown, KY, on the one hand, and, on the other, points in the U.S. (except AK and HI).

**Note.**—The purpose of this application is to substitute motor carrier for abandoned rail carrier service.

MC 129420 (Sub-6), filed May 5, 1982. Applicant: LILE INTERNATIONAL COMPANIES, 15605 S.W. 72nd Avenue, Tigard, OR 97223. Representative: Wendell B. Lile (same address as applicant) (503) 620–8480. Transporting *shipments weighing 100 pounds or less* if transported in a motor vehicle in which no one package exceeds 100 pounds, between points in the U.S.

MC 161580, filed April 20, 1982. Applicant: HAROLD W. LIGGETT, d.b.a. OGALLALA PRODUCE, 1305 Debra Lane, Madison, WI 53704. Representative: Charles E. Dye, Swan Lake Village, Saddle Ridge #832, Portage, WI 53901; (608) 742–3579. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers, and other soil conditioners,* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

MC 161811, filed May 3, 1982. Applicant: LEASING AND MAINTENANCE, INC., 3842 West St., Landover, MD 20785. Representative: Gerald K. Gimmel, Suite 200, 444 N. Frederick Ave., Gaithersburg, MD 20877; (301) 840–8565. Transporting (1) for or on behalf of the United States Government, *general commodities* (except used household goods, hazardous or secret materials, and sensitive weapons and munitions), and (2) *shipments weighing 100 pounds or less* if transported in a motor vehicle in which no one package exceeds 100 pounds, between points in the U.S. (except AK and HI).

MC 161820, filed May 4, 1982. Applicant: F & D EPPENBACH TRUCKING, INC., P.O. Box 570, Blair, NE 68008. Representative: James F. Crosby, 7363 Pacific Street, Suite 210B, Omaha, NE 68114; (402) 397–9900. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *Agricultural limestone, and fertilizers, and other soil conditioners* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

#### Volume No. OP2–98

Decided: May 7, 1982.

By the Commission, Review Board No. 1, Members Parker, Chandler, and Fortier.

MC 144122 (Sub-84), filed April 26, 1982. Applicant: CARRETTA TRUCKING, INC., South 160, Route 17 North, Paramus, NJ 07652. Representative: Charles J. Williams, P.O. Box 186, Scotch Plains, NJ 07076; (201) 322–5030. As a broker of *general commodities* (except household goods), between points in the U.S. (including AK, but excluding HI).

MC 157763 (Sub-1), filed April 20, 1982. Applicant: PRESTO TRANSPORTATION, INC., P.O. Box 469, Peru, IL 61354. Representative: David Earl Tinker, 100 Connecticut Avenue, NW., Suite 1112, Washington, DC 20036-5391, (202) 887-5868. (1) Transporting, for or on behalf of the United States Government, *general commodities* (except used household goods, hazardous or secret materials, and sensitive weapons and munitions), between points in the U.S. (except AK and HI) (2) transporting *shipments weighing 100 pounds or less* if transported in a motor vehicle in which no one package exceeds 100 pounds, between points in the U.S. (except AK and HI), and (3) as a *broker of general commodities* (except household goods), between points in the U.S. (except AK and HI).

MC 161752, filed April 30, 1982. Applicant: TOP-TOW TOWING CORPORATION, 111 West Washington Street, Chicago, IL 60606. Representative: Charles H. Wickman, Suite 1435, 2 North Riverside Plaza, Chicago, IL 60606, (312) 454-0220. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agriculture limestone and fertilizers, and other soil conditioners* by owner of motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

**Volume No. OP2-104**

Decided: May 18, 1982.

By the Commission, Review Board No. 1, Members Parker, Chandler, and Fortier.

MC 151803 (Sub-2), filed May 6, 1982. Applicant: SOUTHERN EXPRESS, INC., 860 West Main St., Spartanburg, SC 29301. Representative: Joseph M. Epting, 1338 Main St., P.O. Box 11414, Columbia, SC 29211, (803) 799-9427. Transporting for or on behalf of the United States Government, *general commodities* (except used household goods, hazardous or secret materials, and sensitive weapons and munitions), between points in the U.S. (except AK and HI).

MC 161852 (Sub-2), filed May 6, 1982. Applicant: TROPHY TRANSPORT, INC., P.O. Box 2352, Dalton, GA 30720. Representative: Gerald K. Gimmel, Suite 200, 444 N. Frederick Ave., Gaithersburg, MD 20877, 301-840-8565. Transporting, for or on behalf of the United States Government, *general commodities* (except used household goods, hazardous or secret materials, and sensitive weapons and munitions), between points in the U.S. (except AK and HI).

MC 161893, filed May 10, 1982. Applicant: ADVANCED WAREHOUSE AND DISTRIBUTION CORPORATION, 30 Middlesex Ave., Somerville, MA 02145. Representative: James F. Martin, Jr., 8 W. Morse Rd., Bellingham, MA 02019, 617-966-2093. As a *broker* of *general commodities* (except household goods), between points in the U.S. (except AK and HI).

**Volume No. OP2-101**

Decided: May 14, 1982.

By the Commission, Review Board No. 1, Members Parker, Chandler, and Fortier.

MC 139253 (Sub-9), filed April 28, 1982. Applicant: SOUTHEASTERN WAREHOUSING AND DISTRIBUTION CORPORATION, 102 Ashe St., Johnson City, TN 37061. Representative: Roland M. Lowell, 5th Floor, 501 Union St., Nashville, TN 37219, 615-255-0540. Transporting, for or on behalf of the United States Government, *general commodities* (except used household goods, hazardous or secret materials and sensitive weapons and munitions) and *used household goods* for the account of the United States Government incident to the performance of a pack-and-crate service on behalf of the Department of Defense, between points in the U.S. (except AK and HI).

MC 147342 (Sub-1), filed May 5, 1982. Applicant: FOSTER'S TRANSPORTATION, INC., Mullica Hill Road, Box 10, R.D. 3, Woodstown, NJ 93924. Representative: Lawrence Marquette, P.O. Box 629, Carmel Valley, CA 93924, (408) 625-2031. (1) Transporting, for or on behalf of the United States Government, *general commodities* (except used household goods, hazardous or secret materials, and sensitive weapons and munitions), between points in the U.S. (except AK and HI); (2) As a *broker of general commodities* (except household goods), between points in the U.S. (except AK and HI); (3) Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers, and other soil conditioners,* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

MC 148103 (Sub-2), filed April 28, 1982. Applicant: BIG JOHN TRANSPORTATION COMPANY, 5805 Greenash, Houston, TX 77081. Representative: John W. Carlisle, P.O. Box 967, Missouri City, TX 77459, 713-437-1768. Transporting, for or on behalf of the United States Government, *general commodities* (except used household goods, hazardous or secret materials and sensitive weapons and munitions), between points in the U.S. (except AK and HI); (2) *Shipments weighing 100 pounds or less* if transported in a motor vehicle in which no one package exceeds 100 pounds, between points in the U.S. (except AK and HI); (3) As a *broker of general commodities* (except household goods), between points in the U.S. (except AK and HI); (4) *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers, and other soil conditioners* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI); and (5) *used household goods* for the account of the United States Government incident to the performance of a pack-and-crate service on behalf of the Department of Defense, between points in the U.S. (except AK and HI).

MC 161543, filed April 15, 1982. Applicant: AGRICULTURAL EXPRESS OF AMERICA, 3409 West Pershing Road, Chicago, IL 60632. Representative: Charles A. Webb, 1828 L St., NW., Washington, DC 20036, (202) 822-8200. As a *broker of general commodities* (except household goods) between points in the U.S. (including AK and HI).

**Volume No. OP2-103**

Decided: May 13, 1982.

By the Commission, Review Board No. 1, Members Parker, Chandler, and Fortier. (Member Parker not participating.)

MC 129623 (Sub-6), filed April 15, 1982. Applicant: FRANK E. HUGHES, d.b.a. HUGHES MOVING & STORAGE CO., P.O. Box 5187, Huntsville, AL 35805. Representative: Ronald L. Stichweh, 727 Frank Nelson Bldg., Birmingham, AL 35203, (205) 251-5223. Transporting *used household goods* for the account of the United States Government incident to the performance of a pack-and-crate service on behalf of the Department of Defense, between points in the U.S. (except AK and HI).

MC 161783, filed April 30, 1982. Applicant: DALE E. HOOVER, Box 151 R.D. #3, Lititz, PA 17543. Representative: Dale E. Hoover (same address as above) (717) 626-6435. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers, and other soil conditioners* by the owner of the motor vehicle in such vehicle; between points in the U.S. (except AK and HI).

MC 161823, filed May 3, 1982. Applicant: LE-HI AGENCY, INC., 11

Westward Circle, Van Buren, AR 72956. Representative: Gerald K. Gimmel, Suite 200, 444 N. Frederick Ave., Gaithersburg, MD 20877; (301) 840–8565. As a *broker of general commodities,* (except household goods), between points in the U.S. (except AK and HI).

**Volume No. OP3–077**

Decided: May 18, 1982.

By the Commission, Review Board No. 2, Members Carleton, Fisher, and Williams.

MC 161605, filed April 21, 1982. Applicant: WILLIAM D. CRITES d.b.a. RAINBOW TRANSPORTATION, 1314 Emporia St., Aurora, CO 80010. Representative: William D. Crites (same address as applicant) (303) 341–1950. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers, and other soil conditioners* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

MC 161855, filed May 6, 1982. Applicant: GEORGE REISLER d.b.a. COMMUNITY TRUCKING CO., 443 Calmosa Dr., Port St. Lucie, FL 33452. Representative: Barry Weintraub, Suite 510, 8133 Leesburg Pike, Vienna, VA 22180; (703) 442–8330. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers, and other soil conditioners* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

**Volume No. OP5–109**

Decided: May 12, 1982.

By the Commission, Review Board No. 3, Members Krock, Joyce, and Dowell.

MC 161629, filed April 22, 1982. Applicant: WILLIAM J. FULLER, Rt. 2, Box 392–A, West Monroe, LA 71291. Representative: William J. Fuller (same address as above.) (318) 396–2215. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers, and other soil conditioners* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

MC 161659, filed April 26, 1982. Applicant: EXCEL TRAFFIC CONSULTANTS, P.O. Box 61664, Dallas/Fort Worth Airport, TX 75261. Representative: Martin Perez, 3917 Wind River Ct., Irving, TX 75062; (214) 255–8257. To operate as a *broker* of *general commodities* (except household goods), between points in the U.S. (except AK and HI).

MC 161829, filed May 4, 1982. Applicant: MARYLAND OVERPAK CORPORATION, 1301 Wicomico St., Baltimore, MD 21230. Representative: George Herzog, Jr. (same address as applicant) 301–539–6620. As a *broker of general commodities* (except household goods), between points in the U.S. (except AK and HI).

**Volume No. OP5–111**

Decided: May 14, 1982.

By the Commission, Review Board No. 3, Members Krock, Joyce, and Dowell.

MC 161819, filed May 4, 1982. Applicant: SAVANNAH FAST FREIGHT, INC., P.O. Box 2665, Savannah, GA 31402. Representative: Richard E. Mobley (same address as applicant) (912) 236–9661. To operate as a *broker* of *general commodities* (except household goods), between points in the U.S. (except AK and HI).

MC 161839, filed May 5, 1982. Applicant: TRANS AMERICA COURIER SYSTEMS, INC., 74–09 37th Ave., Jackson Heights, NY 11372. Representative: Michael R. Werner, 241 Cedar Lane, Teaneck, NJ 07666; 201–836–1144. Transporting *shipments weighing 100 pounds or less* if transported in a motor vehicle in which no one package exceeds 100 pounds, between points in the U.S. (except AK and HI).

MC 161849, filed May 6, 1982. Applicant: J.D.L. TRUCK SERVICE, INC., 1090 Industrial Dr., Bensenville, IL 60106. Representative: Barry Weintraub, Suite 510, 8133 Leesburg Pike, Vienna, VA 22180; 703–442–8330. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers, and other soil conditioners* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

MC 161859, filed May 6, 1982. Applicant: LOAD LOCATORS LTD., P.O. Box 1908, Des Moines, IA 50306. Representative: Donald B. Strater, 1350 Financial Center, Des Moines, IA 50309; (515) 283–2411. To operate as a *broker* of *general commodities* (except household goods), between points in the U.S. (except AK and HI).

**Agatha L. Mergenovich,**

*Secretary.*

[FR Doc. 82–14175 Filed 5–24–82; 8:45 am]

BILLING CODE 7035–01–M

**[Docket No. AB–1 (Sub-128)]**

## Rail Carriers; Chicago and North Western Transportation Co.—Abandonment—Between Cannon Falls and Red Wing, MN; Findings

The Commission has found that the public convenience and necessity permit Chicago and North Western Transportation Company to abandon its 20.5 mile line of railroad between Cannon Falls, MN (milepost 74.3) and Red Wing, MN (milepost 94.8), in Goodhue County, MN. A certificate will be issued authorizing this abandonment unless within 15 days after this publication the Commission also finds that: (1) a financially responsible person has offered assistance (through subsidy or purchase) to enable the rail service to be continued; and (2) it is likely that the assistance would fully compensate the railroad.

Any financial assistance offer must be filed with the Commission and served concurrently on the applicant, with copies to Mr. Louis Gitomer, Room 5417, Interstate Commerce Commission, Washington, DC 20423, no later than 10 days from publication of this Notice. Any offer previously made must be remade within this 10 day period.

Information and procedures regarding financial assistance for contined rail services are containued in 49 U.S.C. 10905 and 49 CFR 1121.38.

**Agatha L. Mergenovich,**

*Secretary.*

[FR Doc. 82–14173 Filed 5–24–82; 8:45 am]

BILLING CODE 7035–01–M

## DEPARTMENT OF JUSTICE

## Notice of Proposed Consent Decree in Action To Enjoin Discharge of Water Pollutants

In accordance with Departmental Policy, 28 CFR 50.7, 38 FR 19029, notice is hereby given that a proposed consent decree in *United States of America* v. *City of Glendale, Colorado,* Civil No. 80–C–874, was lodged on May 6, 1982 with the District Court for the District of Colorado. The proposed decree would effect settlement of the United States' complaint alleging violation of the NPDES permit requirement by the City.

The Department will receive for a period of thirty (30) days from the date of this notice written comments relating to the proposed consent decree. Comments should be addressed to the Assistant Attorney General of the Land and Natural Resources Division, Department of Justice, Tenth and Pennsylvania Avenue, N.W.,

Washington, D.C. 20530, and should refer to *United States of America* v. *City of Glendale, Colorado,* DJ Ref. No. 90-5-1-1-1417.

A copy of the proposed consent decree may be examined at: (1) The Office of the United States Attorney, District of Colorado (Attention: Assistant United States Attorney James Winchester), 1200 Federal Building, 1961 Stout Street, Denver, Colorado 80294; (2) the Region VIII Office of the U.S. Environmental Protection Agency, (Attention: Regional Counsel) (E-8) 1860 Lincoln Street, Denver, Colorado 80203; and (3) the Environmental Enforcement Section, Land and Natural Resources Division, U.S. Department of Justice, Room 1515, Ninth and Pennsylvania Avenue, N.W., Washington, D.C. 20530. A copy of the proposed consent decree may be obtained in person or by mail from the Environmental Enforcement Section, Land and Natural Resources Division, U.S. Department of Justice. In order to cover the reproduction costs, all requests for copies must be accompanied by a check or money order in the amount of $1.20 (10 cents per page) payable to the Treasurer of the United States.

**Carol E. Dinkins,**

*Assistant Attorney General, Land and Natural Resources Division.*

[FR Doc. 82-14308 Filed 5-24-82; 8:45 am]

BILLING CODE 4410-01-M

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### Competitive Grant Solicitation

The National Institute of Justice announces a competitive grant solicitation for research on the use and effects of laws which permit public safety to be used as a criterion in pretrial releasedecision-making. Issues to be addressed include:

1. The nature of these laws and the administrative requirements for their use.
2. The extent of their use in selected jurisdictions.
3. The effects of their use on individual defendants, the jail population, and, if possible on pretrial crime.

Applicants are encouraged to propose appropriate approaches for addressing these issues.

The solicitation requests submission of proposals which will then be considered by a peer review panel. In order to be considered, proposals must be received no later than July 2, 1982. A total of $300,000 has been allocated for this research, which may extend for up to two years.

Additional information and copies of the solicitation may be obtained by contacting: National Criminal Justice Reference Service, Box 6000, Rockville, Maryland 20850.

Please specify "Pretrial Release" solicitation and enclose a self-addressed mailing label.

Dated: May 12, 1982.

**James L. Underwood,**

*Acting Director, National Institute of Justice.*

[FR Doc 82-14156 Filed 5-24-82; 8:45 am]

BILLING CODE 4410-18-M

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## National Institute of Justice

### Competitive Grant Solicitation

The National Institute of Justice announces a competitive grant solicitation for research on the use and effects of those sentence laws designed to increase the penalty imposed on certain convicted offenders. Among such laws are those aimed at habitual offenders and those allowing consecutive sentencing for multiple offenses. The three primary issues to be addressed are:

1. The types of such sentence enhancement laws which are available for use in the United States.
2. The extent and nature of their use in selected jurisdictions.
3. The more immediate effects of the use on individual offenders and on the courts and correctional system.

Applicants are encouraged to propose appropriate approaches for addressing these issues.

The solicitation requests submission of proposals which will then be considered by a peer review panel. In order to be considered, proposals must be received no later than July 7, 1982. A total of $250,000 has been allocated for this research, which may extend for up to two years.

Additional information and copies of the solicitation may be obtained by contacting: National Criminal Justice Reference Service, Box 6000, Rockville, Maryland 20850; 301/251-5500.

Please specify "Use of Sentence Enhancement Laws" solicitation and enclose a self-addressed mailing label.

Dated: May 14, 1982.

**James L. Underwood,**

*Acting Director, National Institute of Justice.*

[FR Doc. 82-14155 Filed 5-24-82; 8:45 am]

BILLING CODE 4410-18-M

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## DEPARTMENT OF LABOR

## Occupational Safety and Health Administration

### Oregon State Standards; Approval

1. *Background.* Part 1953 of Title 29, Code of Federal Regulations prescribes procedures under section 18 of the Occupational Safety and Health Act of 1970 (hereinafter called the Act) by which the Regional Administrator for Occupational Safety and Health (hereinafter called Regional Administrator) under a delegation of authority from the Assistant Secretary of Labor for Occupational Safety and Health (hereinafter called the Assistant Secretary) (29 CFR 1953.4) will review and approve standards promulgated pursuant to a State plan which has been approved in accordance with section 18(c) of the Act and 29 CFR Part 1902. On December 28, 1972, notice was published in the **Federal Register** (37 FR 28628) of the approval of the Oregon plan and the adoption of Subpart D to Part 1952 containing the decision. The Notice of Approval of Revised Developmental Schedule was further published on April 1, 1974 in the **Federal Register** (39 FR 11881).

The Oregon plan provides for the adoption of State standards which are at least as effective as comparable Federal standards promulgated under section 6 of the Act. Section 1953.20 provides that "Where any alteration in the Federal program could have an adverse impact on the at least as effective as" status of the State program, a program change supplement to a State plan shall be required.

In response to Federal standards changes, the State has submitted by letter dated July 30, 1981 from Darrel D. Douglas to James W. Lake and incorporated as part of the plan, an amendment to revoke State standards comparable to the revocation of 29 CFR 1910.263, Bakery Equipment, as published in the **Federal Register** (43 FR 51760) dated October 24, 1978 and subsequent corrections in the **Federal Register** (43 FR 51760) dated November 7, 1978.

These State standards which were originally contained in OAR 437, Chapter 30, received OSHA approval and notice to that effect was published in the **Federal Register** (40 FR 36817) dated August 22, 1975.

The State's revocations became a final order after public notice through the State Administrative Rules Bulletin published on October 15, 1980 and by

direct mail to concerned parties. Both actions failed to elicit requests for a public hearing. As part of the amendment, the State standards have been renumbered to OAR 437, Division 77; and editorial changes, consisting of the rewording of several of the remaining standards, have been made.

2. *Decision.* Having reviewed the State submission in comparison with the Federal standards, it has been determined that the State standards revocations are identical to the comparable Federal standards revocations. The remaining standards, which have been reworded, are at least as effective as the comparable Federal standards. There are no significant areas of differences. Accordingly the Oregon Standards, OAR 437, Division 77, Baking Equipment, should be approved.

3. *Location of supplement for inspection and copying.* A copy of the standards supplement, along with the approved plan, may be inspected and copied during normal business hours at the following locations: Office of the Regional Administrator, Occupational Safety and Health Administration, Room 6003, Federal Office Building, 909 First Avenue, Seattle, Washington 98174; Workers' Compensation Board, Labor and Industries Building, Salem, Oregon 97310; and the Office of State Programs, Room N3613, 200 Constitution Avenue N.W., Washington, D.C. 20210.

4. *Public participation.* Under 29 CFR 1953.2(c) the Assistant Secretary may prescribe alternative procedures to expedite the review process or for other good cause which may be consistent with applicable laws. The Assistant Secretary finds that good cause exists for not publishing the supplement to the Oregon plan as a proposed change and making the Regional Administrator's approval effective upon publication for the following reason:

The standards were adopted in accordance with the procedural requirements of State law which included opportunity for public comment and further public participation would be repetitious.

This decision is effective May 25, 1982.

(Sec. 18, Pub. L. 91-596, 84 Stat. 1608 (29 U.S.C. 667))

Signed at Seattle, Washington this 10th day of December, 1981.

**Ronald T. Tsunehara,**

*Acting Regional Administrator.*

[FR Doc. 82-14214 Filed 5-24-82; 8:45 am]

BILLING CODE 4510-26-M

## MERIT SYSTEMS PROTECTION BOARD

### Air Traffic Controller Appeals

**AGENCY:** Merit Systems Protection Board.

**ACTION:** Notice.

**SUMMARY:** Notice is hereby given that the Merit Sytems Protection Board intends to complete action on approximately 11,000 appeals from air traffic controllers on or before December 31, 1982. This completion date is established with the expectation that a request for supplemental funding for fiscal year 1982, currently before the Congress, will be granted soon.

This notice revokes a prior notice in 47 FR 7898 (1982) which set September 1, 1982, as the anticipated completion date of air traffic controller appeals. The prior notice was predicated on receipt of the supplemental funding early in calendar year 1982.

Due to insufficient funds with which to staff properly its regional offices and provide for hearing officers to travel to conduct hearings, the Board has been unable to adjudicate these appeals as expeditiously as it had anticipated.

This notice constitutes the public announcement of a new completion date required by 5 U.S.C. 7701(i)(1).

**DATES:** New completion date: December 31, 1982.

**FOR FURTHER INFORMATION CONTACT:** Michael W. Doheny, (202) 653-7980.

Dated: May 21, 1982.

For the Board.

**Herbert E. Ellingwood,**

*Chairman.*

[FR Doc. 82-14322 Filed 5-24-82; 8:45 am]

BILLING CODE 7400-01-M

## NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

**[Notice (82-30)]**

### NASA Advisory Council, Aeronautics Advisory Committee; Meeting

**AGENCY:** National Aeronautics and Space Administration.

**ACTION:** Notice of meeting.

**SUMMARY:** In accordance with the Federal Advisory Committee Act., Pub. L. 92-463, as amended, the National Aeronautics and Space Administration announces a forthcoming meeting of the NASA Advisory Council, Aeronautics Advisory Committee, Informal Advisory Subcommittee on Safety, Human Factors, and Operating Systems.

**DATE AND TIME:** June 15, 1982, 9 a.m. to 5 p.m.; June 16, 1982, 8:30 a.m. to 5 p.m.

**ADDRESS:** NASA Langley Research Center, Building 1244, Room 223, Hampton, VA.

**FOR FURTHER INFORMATION CONTACT:** Mr. Roger Winblade, National Aeronautics and Space Administration, Code RJT-2, Washington, D.C. 20546; (202/755-3000).

**SUPPLEMENTARY INFORMATION:** The Informal Advisory Subcommittee on Safety, Human Factors, and Operating Systems has been established to assist the NASA in assessing the current adequacy of transport aircraft technology and recommend actions to reduce deficiencies through modification of the planned NASA resesrch and technology program in transport safety, human factors, and operating systems. The Subcommittee, chaired by Mr. J. D. Smith, is comprised of thirteen members. The meeting will be open to the public up to the seating capacity of the room (approximately 40 persons including the Subcommittee members and participants).

Type of Meeting: Open.

Agenda:

June 15, 1982

9 a.m.—Opening Remarks.

9:15 a.m.—Summary of NASA Budget Situation and Philosophy for Future Aeronautics Programs.

10 a.m.—NASA Aeronautics Long Range Plan.

11 a.m.—NASA Advanced Transport Operating Systems Research.

5 p.m.—Adjourn.

June 16, 1982

8:30 a.m.—NASA Human Factors Research.

2 p.m.—NASA Safety Technology Research.

4 p.m.—Discussion of NASA Research Program—Scope, Content, and Critical Issues.

4:30 p.m.—Subcommittee Recommendations on NASA Research Program and Areas for Possible Future Discussion.

**Nathaniel B. Cohen,**

*Director, Management Support Office, Office of External Relations.*

May 19, 1982.

[FR Doc. 82-14160 Filed 5-24-82; 8:45 am]

BILLING CODE 7510-01-M

## SECURITIES AND EXCHANGE COMMISSION

**[Release No. 12439; 811-2748]**

### Federated Option Income Fund, Inc.; Filing of an Application

May 18, 1982.

In the matter of Federated Option Income Fund, Inc., 421 Seventh Avenue, Pittsburgh, Pennsylvania 15219 (811-2748).

Notice is hereby given that Federated Option Income Fund, Inc. ("Applicant"), registered as an open-end, diversified, management investment company under the Inventment Company Act of 1940 ("Act"), filed an application on March 29, 1982, for an order pursuant to Section 8(f) of the Act, declaring that it has ceased to be an investment company as defined in the Act. All interested persons are referred to the application on file with the Commission for a statement of the representations contained therein, which are summarized below.

Applicant was organized under the laws of Maryland on September 15, 1975. On May 18, 1977, it registered under the Act and filed a registration statement pursuant to the Securities Act of 1933 to register 2,000,000 shares of its capital stock. That registration statement was made effective on June 17, 1977, and a public offering of Applicant's securities commenced on that date.

On November 19, 1981, Applicant's board of directors authorized the merger of Applicant into Federated High Income Securities, Inc. ("Federated High"), and on February 19, 1982, at a meeting of Applicant's shareholders, the merger was approved by the shareholders by a vote of 768,945.585 in favor of the merger to 19,884.310 in opposition. On that date Applicant had outstanding 1,137,009.092 shares of common stock having an aggregate net asset value of $13,757,811.12, or $12.10 per share. On February 22, 1982, Applicant's assets were transferred to Federated High in exchange for shares of Federated High on the same basis as held by Applicant and subsequently distributed to Applicant's shareholders. Expenses of the merger were allocated between Applicant and Federated High in proportion to their respective net assets as February 19, 1982, of which Applicant's portion was $8,532.97.

The application states that Applicant is not a party to any litigation or administrative proceeding; and that no separate trust has been created to hold any of its assets, and that it has no assets, debts or liabilities outstanding. Applicant represents that the Articles of Merger were filed with the Maryland Department of Assessments and Taxation on February 22, 1982; that Applicant's corporate existence was terminated as of February 22, 1982; that Applicant now has no securityholders, and that it is not engaged in any business.

Section 8(f) of the Act provides, in pertinent part, that whenever the Commission, on its own motion or upon application, finds that a registered investment company has ceased to be an investment company, it shall so declare by order, and upon the effectiveness of that order the registration of such company shall cease to be in effect.

Notice is further given that any interested person may, not later than June 11, 1982, at 5:30 p.m., submit to the Commi;ssion in writing a request for a hearing on this matter accompanied by a statement as to the nature of his interest, the rason for such request, and the issues of fact or law proposed to be controverted, or he may request that he be notified if the Commission shall order a hearing thereon. Any such communication should be addressed: Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of such request shall be served personally or by mail (air mail if the person being served is located more than 500 miles from the point of mailing) upon the Applicant at the address stated above. Proof of such service (by affidavit, or in the case of an attorney-at-law, by certificate) shall be filed contemporaneously with the request. As provided by Rule O-5 of the Rules and Regulations promulgated under the Act, an order disposing of the application herein will be issued as of course following said date unless the Commission thereafter orders a hearing upon request or upon the Commission's own motion. Persons who request a hearing or advice as to whether a hearing is ordered will receive any notices and orders issued in this matter, including the date of the hearing (if ordered) and any postponements thereof.

For the Commission, by the Division of Investment Management, pursuant to delegated authority.

**Shirley E. Hollis,**

*Assistant Secretary.*

[FR Doc. 82-14195 Filed 5-24-82; 8:45 am]

BILLING CODE 8010-01-M

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**[Release No. 12437; 812-5179]**

## NEL Cash Management Trust; Filing of Application

May 17, 1982.

In the matter of NEL Cash Management Trust (formerly NEL Cash Management Account, Inc.), 501 Boylston Street, Boston, Massachusetts 02117 (812-5179).

Notice is hereby given that NEL Cash Management Trust (formerly NEL Cash Management Account, Inc.) ("Applicant") an open-end diversified management investment company, filed an application on April 23, 1982, and an amendment thereto on May 10, 1982, requesting an order of the Commission pursuant to Section 6(c) of the Investment Company Act of 1940 (the "Act") amending a prior order of the Commission to exempt Applicant from Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 thereunder, to the extent necessary to permit Applicant to value the assets held in its U.S. Government Series and its Money Market Series using the amortized cost method of valuation. All interested persons are referred to the application on file with the Commission for a statement of the representations contained therein, which are summarized below.

Applicant states that it is a Massachusetts business trust which was organized to continue the business of its predecessor, NEL Cash Management Account, Inc. (the "Company"). The Commission issued an order on October 31, 1979 (Investment Company Release No. 10926), pursuant to Section 6(c) of the Act, exempting the Company from Rules 2a-4 and 22c-1 under the Act to the extent necessary to permit the Company to value its portfolio assets pursuant to the amortized cost method of valuing portfolio securities. The application states that Applicant seeks to register a second series of its shares and thereby to become a so-called series fund. In order to avoid any question as to the scope of the existing order, Applicant filed this application pursuant to Section 6(c) of the Act for an amended order to exempt Applicant from Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 thereunder to the extent necessary to permit Applicant to use the amortized cost method of valuation for the purpose of valuing the portfolio securities of each of its two series.

Applicant states that its Trustees have recently approved the creation of a new series of shares, the U.S. Government Series ("Government Series"), which will invest only in short-term obligations of the United States Government and related repurchase agreements. Its investment objective is to seek the highest current income consistent with maximum safety of capital and liquidity. The existing assets of the Applicant are to be redesignated as the Money Market Series upon the creation of the Government Series. The application states that the Money Market Series will continue to invest in high quality money market instruments in accordance with Applicant's current investment objective, which is to provide maximum

current income consistent with preservation of capital and liquidity.

The application states that assets received by the Applicant for the issue or sale of shares of each series and all income earnings, profits, losses, and proceeds derived from such assets will be allocated to that series. The application further states that the underlying assets of each series will be segregated and charged with the expenses in respect of that series and with its share of the general expenses of the Applicant. Any general expenses of the Applicant not readily identifiable as belonging to a particular series will be allocated by the Trustees in such manner as the Trustees determine to be be fair and equitable. The net income of each series will be determined, and dividends will be declared and paid, separately for each series based upon the interest, discounts, gains, losses, premium, and expenses attributable to such series.

Applicant states that its Trustees have concluded that it is in the best interests of the shareholders of each series to use the amortized cost method of valuing each series' portfolio securities to maintain a constant net asset value per share for each series at $1.00. Applicant states that the continued use of amortized cost valuation for each series would, in addition, offer the shareholders of such series the convenience of being able to value their investments in any series simply by knowing the number of shares that they own of that series.

As here pertinent, Section 2(a)(41) of the Act defines value to mean: (1) with respect to securities for which market quotations are readily available, the market value of such securities, and (2) with respect to other securities and assets, fair value as determined in good faith by the board of directors. Rule 22c-1 adopted under the Act provides, in part, that no registered investment company or principal underwriter therefor issuing any redeemable security shall sell, redeem or repurchase any such security except at a price based on the current net asset value of such security which is next computed after receipt of a tender of such security for redemption or of an order to purchase or sell such security. Rule 2a-4 adopted under the Act provides, as here relevant, that the "current net asset value" of a redeemable security issued by a registered investment company used in computing its price for the purposes of distribution, redemption and repurchase shall be an amount which reflects calculations made substantially in accordance with the provisions of that rule, with estimates used where necessary or appropriate. Rule 2a-4 states further that portfolio securities with respect to which market quotations are readily available shall be valued at current market value, and other securities and assets shall be valued at fair value as determined in good faith by an investment company's board of directors. Prior to the filing of this application, the Commission expressed its view that, among other things: (1) Rule 2a-4 under the Act requires portfolio instruments of "money market" funds which have more than 60 days remaining to maturity be valued with reference to market factors and (2) it would be inconsistent with the provisions of Rule 2a-4 for a "money market" fund to value its portfolio instruments with over sixty-day maturities on an amortized cost basis (Investment Company Act Release No. 9786, May 31, 1977).

Section 6(c) of the Act provides, in pertinent part, that the Commission, by order upon application, may conditionally or unconditionally exempt any person, security or transaction, or any class or classes of persons, securities or transactions from any provision of the Act, if and to the extent that such exemption is necessary or appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act.

Applicant has agreed that each of the following may be made a condition to granting the exemptive relief requested:

1. In supervising the operations of each of Applicant's series and in delegating special responsibilities involving portfolio managment to the respective investment advisers of each series, Applicant's Trustees undetake—as a particular responsibility within the overall duty of care owed to shareholders of each series—to establish procedures reasonably designed, taking into account current market conditions and the investment objectives of each series, to stabilize the net asset value per share of each of Applicant's series, as computed for the purpose of distribution, redemption and repurchase, at $1.00 per share.

2. Included within the procedures to be adopted by Applicant's Trustees shall be the following:

(a) Review by the Trustees, as they deem appropriate and at such intervals as are reasonable in light of current market conditions, to determine, with respect to each series, the extent of deviation, if any, of the net asset value per share of such series, as determined by using available market quotations, from the $1.00 amortized cost price per share of such series, and the maintenance of records of such review.

(b) In the event that the net asset value per share of any series, determined as set forth in condition 2(a), deviates from the $1.00 amortized cost price per share of such series by more than ½ of 1%, a requirement that the Trustees will promptly consider what action, if any, should be initiated.

(c) Where the Trustees believe that the extent of any deviation from the $1.00 amortized cost price per share of any series may result in material dilution or other unfair results to investors or existing shareholders of that series, they shall take such action as they deem appropriate to eliminate or to reduce to the extent reasonably practicable such dilution or unfair results, which action may include: redemption of shares in kind; selling portfolio instruments prior to maturity to realize capital gains or losses, or to shorten the average portfolio maturity of the relevant series; withholding dividends; or utilizing a net asset value per share of the revelant series as determined by using available market quotations.

3. Applicant will maintain for each series a dollar-weighted average portfolio maturity appropriate to its objective of maintaining a stable net asset value per share; provided, however, that no series will (a) purchase any instrument with a remaining maturity of greater than one year, or (b) maintain a dollar-weighted average portfolio maturity that exceeds 120 days. In fulfilling this condition, Applicant agrees that if the disposition of a portfolio instrument should result in a dollar-weighted average portfolio maturity in excess of 120 days for a series, such series will invest its available cash in such a manner as to reduce its dollar-weighted average portfolio maturity to 120 days or less as soon as reasonably practicable.

4. Applicant will record, maintain, and preserve, on behalf of each series, permanently in an easily accessible place, a written copy of the procedures (and any modifications thereto) described in condition 1 above; and Applicant will record, maintain, and preserve for a period of not less than six years (the first two years in an easily accessible place) a written record of the Trustees' considerations and actions taken in connection with the discharge of their responsibilities, as set forth above, to be included in the minutes of the Trustees' meetings. The documents preserved pursuant to this condition

shall be subject to inspection by the Commission in accordance with Section 31(b) of the Act as though such documents were records required to be maintained pursuant to rules adopted under Section 31(a) of the Act.

5. Applicant will limit the portfolio investments, including repurchase agreements, of each series to those U.S. dollar-denominated instruments which the Trustees determine present minimal credit risks, and which are of high quality as determined by any major rating service or, in the case of any instrument that is not rated, of comparable quality as determined by the Trustees.

6. Applicant will include in each quarterly report, as an attachment to Form N-1Q, a statement as to whether any action pursuant to condition 2(c) above was taken during the preceding fiscal quarter, and, if any action was taken, Applicant will describe the nature and circumstances of such action.

Notice is further given that any interested person may, not later than June 9, 1982, at 5:30 p.m., submit to the Commission in writing a request for a hearing on the application accompanied by a statement as to the nature of his interest, the reason for such request, and the issues if any, of fact or law proposed to be controverted, or he may request that he be notified if the Commission shall order a hearing thereon. Any such communication should be addressed: Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of such request shall be served personally or by mail upon Applicant at the address stated above. Proof of such service (by affidavit or, in the case of an attorney-at-law, by certificate) shall be filed contemporaneously with the request. As provided by Rule 0-5 of the Rules and Regulations promulgated under the Act, an order disposing of the application will be issued as of course following said date unless the Commission thereafter orders a hearing upon request or upon the Commission's own motion. Persons who request a hearing, or advice as to whether a hearing is ordered, will receive any notices and orders issued in this matter, including the date of the hearing (if ordered) and any postponements thereof.

For the Commission, by the Division of Investment Management, pursuant to delegated authority.

**Shirley E. Hollis,**

*Assistant Secretary.*

[FR Doc. 82-14197 Filed 5-24-82; 8:45 am]

BILLING CODE 8010-01-M

**[Release No. 18748; SR-PSE-82-3]**

## Pacific Stock Exchange, Inc.; Order Approving Proposed Rule Change

May 17, 1982.

In the matter of The Pacific Stock Exchange, Inc., 618 South Spring Street, Los Angeles, CA 90014 (SR-PSE-82-3).

The Pacific Stock Exchange, Inc. ("PSE") submitted on February 26, 1982, copies of a proposed rule change pursuant to Section 19(b)(1) of the Securities Exchange Act of 1934 (the "Act"), and Rule 19b-4 thereunder, to amend Rule II, Section 3(f) of the PSE rules to provide that, as a condition of an exchange member's being registered as a specialist, a specialist is to engage in a course of dealings for his own account to assist in the maintenance, insofar as reasonably practicable, of a fair and orderly market.[1] In addition, the rule change provides that, if the PSE finds any substantial or continued failure by a specialist to engage in such a course of dealings, the registration of such specialist shall be subject to suspension or revocation by the PSE in one or more of the securities in which he is registered.

Notice of the proposed rule change together with the terms of substance of the proposed rule change was given by the issuance of a Commission Release (Securities Exchange Act Release No. 18519, March 1, 1982) and by publication in the **Federal Register** (47 FR 9623, March 5, 1982). No comments were received with respect to the proposed rule filing.

The Commission finds that the proposed rule change is consistent with the requirements of the Act and the rules and regulations thereunder applicable to a national securities exchange and, in particular, the requirements of Sections 6 and 11 and the rules and regulations thereunder.[2]

It is therefore ordered, pursuant to Section 19(b)(2) of the Act, that the above-mentioned proposed rule change be, and hereby is, approved.

For the Commission, by the Division of Market Regulation pursuant to delegated authority.

**Shirley E. Hollis,**

*Assistant Secretary.*

[FR Doc. 82-14196 Filed 5-24-82; 8:45 am]

BILLING CODE 8010-01-M

[1] The Commission has traditionally interpreted a specialist's duty to maintain a fair and orderly market as requiring a course of conduct which includes dealings for the specialist's own account that are reasonably calculated to contribute to the maintenance of price continuity with reasonable depth and to minimize the effects of a temporary disparity between supply and demand or a temporary distortion of the price relationships between the exchange and other markets. In addition, a specialist's dealings should be restricted so far as possible to those reasonably necessary to permit the specialist to maintain a fair and orderly market, and transactions not part of such a course of dealings are not to be effected by a specialist for his own account.

[2] In Securities Exchange Act Release No. 18157 (October 7, 1981), 46 FR 50639 (October 14, 1981), the Commission's modified the exemptions of the regional stock exchanges, including the PSE, from Rule 11b-1 under the Act, to subject the regional exchanges, as of January 1, 1982, to the provisions of Rule 11b-1 with respect to any securities listed on one or more regional exchanges that are not also listed on either the American or New York Stock Exchange. PSE filed this rule change in response to that release. For the most part, the rule change simply reiterates the language of Rule 11b-1 without providing any detail or specifying the manner in which PSE proposes to implement the general standards in Rule 11b-1. Accordingly, although the Commission finds the proposed rule change to be consistent with the requirements of the Act, the Commission views the rule change as only an initial step to conform PSE's rules with Rule 11b-1, and awaits further amendments by PSE to its rules in connection with its compliance with the requirements of Rule 11b-1. The Commission therefore views the rule change approved herein as an interim measure, pending further amendments by the PSE to its rules relating to specialists' responsibilities. During this interim period, the Commission will deem the PSE's rules to incorporate the specialists' duties enumerated in footnote 1 above, and anticipates that future amendments by the PSE to its rules relating to requirements under Rule 11b-1 will, at a minimum, inlcude the responsibilities set forth in footnote 1.

**[Release No. 34-18746; File No. SR-PHILADEP 82-4]**

## Self-Regulatory Organizations; Proposed Rule Change by Philadelphia Depository Trust Co.; Relating to New Fee Schedule

Pursuant to Section 19(b)(1) of the Securities Exchange Act of 1934, 15 U.S.C. 78s(b)(1), notice is hereby given that on April 27, 1982, Philadelphia Depository Trust Company filed with the Securities and Exchange Commission the proposed rule change as described in items I, II, and III below, which Items have been prepared by the self-regulatory organization. The Commission is publishing this notice to solicit comments on the proposed rule change from interested persons.

### I. Self-Regulatory Organization's Statement of the Terms of Substance of the Proposed Rule Change

Philadelphia Depository Trust Company (PHILADEP) proposes to amend its Rule 22 (Bills Rendered) to refer to a separate published fee schedule. The PHILADEP fees, which has been included in a combined SCCP/PHILADEP rate schedule, will be published separately, although SCCP will continue to be the billing agent for PHILADEP.

In addition, certain PHILADEP fee changes are being instituted as follows:

(1) A separate PHILADEP Account Charge of $50.000 per month is being established.

(2) The fee for legal deposits is being increased from $7.50 to $8.50 per deposit.

(3) A discount on PHILADEP charges of 5% is being established for participants with more than 3,000 but less than 4,000 trades per month, and 10% for participants with 4,000 and over trades per month.

(4) The PHILADEP custody fee is being changed from $0.05 per $1,000 of market value (with a $600.00 maximum per month) to $0.50 per issue per month plus $0.01 per 100 shares (or $4,000 bonds) for holdings of 0–1 million shares; $0.005 per 100 shares (or $4,000 bonds) for holdings of 1–5 million shares; and $0.0025 per 100 shares (or $4,000 bonds) for holdings of over 5 million shares.

(5) A dividend charge of $0.25 is being instituted for each cash or stock dividend or interest payment.

(6) A research fee of $2.00 per copy for all photocopies of input forms, etc., requested by participants is being established, as well as a $15.00 per hour charge for research only on items over 1 year old.

The text of proposed rule change and fee schedule are attached to the filing as Exhibit A.

**II. Self-Regulatory Organization's Statement of the Purpose of, and Statutory Basis for, the Proposed Rule Change**

In its filing with the Commission, the self-regulatory organization included statements concerning the purpose of and basis for the proposed rule change and discussed any comments it received on the proposed rule change. The text of these statements may be examined at the places specified in Item IV below. The self-regulatory organization has prepared summaries, set forth in Sections (A), (B), and (C) below, of the most significant aspects of such statements.

*A. Self-Regulatory Organization's Statement of the Purpose of, and Statutory Basis for, the Proposed Rule Change*

While SCCP will continue as the billing agent for PHILADEP, it is appropriate that PHILADEP fees be shown as a separate published schedule of charges. The rewording of PHILADEP Rule 22 refers to this published schedule.

The proposed fee changes on the whole are designed to offset increases in operating costs, especially in labor-intensive areas. The valuation of the custody fee is being changed from a market value basis to a per issue and per share basis, since safekeeping costs do not fluctuate with a rise or fall in market value. In addition, the monthly maximum charge is being eliminated in order that the fee for the larger users more accurately reflects the safekeeping costs. A new rebate against PHILADEP charges is being instituted in conjunction with a reduction in the SCCP volume discount on trade recording charges. The change is being made in order that full SCCP/PHILADEP settling participants may receive some discount on PHILADEP charges as a result of their greater trading volume and revenues generated in supporting the SCCP/PHILADEP clearing and depository system.

The proposed rule change is consistent with the requirements of Section 17A(b)(3)(D) of the Securities Exchange Act of 1934 (the Act) in providing for the equitable allocation of reasonable dues, fees, and other charges among its participants.

*B. Self-Regulatory Organization's Statement on Burden on Competition*

PHILADEP does not perceive any impact on competition, negative or positive, resulting from the proposed rule change.

*C. Self-Regulatory Organization's Statement on Comments on the Proposed Rule Change*

Comments on the proposed rule change have been neither solicited nor received.

**III. Date of Effectiveness of the Proposed Rule Change and Timing for Commission Action**

The foregoing rule change has become effective pursuant to Section 19(b)(3) of the Securities Exchange Act of 1934 and subparagraph (e) of Securities Exchange Act Rule 19b–4. At any time within 60 days of the filing of such proposed rule change, the Commission may summarily abrogate such rule change if it appears to the Commission that such action is necessary or appropriate in the public interest, for the protection of investors, or otherwise in furtherance of the purposes of the Securities Exchange Act of 1934.

**IV. Solicitation of Comments**

Interested persons are invited to submit written data, views and arguments concerning the foregoing. Persons making written submissions should file six copies thereof with the Secretary, Securities and Exchange Commission, 500 North Capitol Street, Washington, D.C. 20549. Copies of the submission, all subsequent amendments, all written statements with respect to the proposed rule change that are filed with the Commission, and all written communications relating to the proposed rule change between the Commission and any person, other than those that may be withheld from the public in accordance with the provisions of 5 U.S.C. 552, will be available for inspection and copying in the Commission's Public Reference Room, 1100 L Street, N.W., Washington, D.C. Copies of such filing will also be avialable for inspection and copying at the principal office of the above-mentioned self-regulatory organization. All submissions should refer to the file number in the caption above and should be submitted by June 16, 1982.

Dated: May 17, 1982.

For the Commission by the Division of Market Regulation, pursuant to delegated authority.

**Shirley E. Hollis,**

*Assistant Secretary.*

[FR Doc. 82-14198 Filed 5-24-82; 8:45 am]

BILLING CODE 8010-01-M

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**[Release No. 34-18747; File No. SR-SCCP 82-4]**

## Self-Regulatory Organizations; Proposed Rule Change by Stock Clearing Corporation of Philadelphia Relating to New Fee Schedule

Pursuant to Section 19(b)(1) of the Securities Exchange Act of 1934, 15 U.S.C. 78s(b)(1), notice is hereby given that on April 27, 1982, Stock Clearing Corporation of Philadelphia filed with the Securities and Exchange Commission the proposed rule change as described in items I, II, and III below, which Items have been prepared by the self-regulatory organization. The Commission is publishing this notice to solicit comments on the proposed rule change from interested persons.

**I. Self-Regulatory Organization's Statement of the Terms of Substance of the Proposed Rule Change**

Stock Clearing Corporation of Philadelphia (SCCP) proposes to amend its Rule 23 (SCCP and PHILADEP Rate Schedule) to remove the Rate Schedule from the rule itself and refer to a separate published rate schedule. Further, the Philadelphia Depository Trust Company fees are being published as a separate schedule, although SCCP

will continue to be the billing agent for PHILADEP.

Two fee changes are also being made at this time:

(1) The volume discount on the $0.80 round lot trade recording fee is being reduced from $0.10 per round lot for 1,000–3,000 round lots per month and $0.20 per round lot for over 3,000 round lots per month to $0.05 and $0.10, respectively.

(2) A research fee of $2.00 per copy for all photocopies of input forms, etc., requested by participants will be assessed, as well as a fee of $15.00 per hour only for research on items over 1 year old.

The text of the proposed rule change and fee schedule are attached to the filing as Exhibit A.

**II. Self-Regulatory Organization's Statement of the Purpose of, and Statutory Basis for, the Proposed Rule Change**

In its filing with the Commission, the self-regulatory organization included statements concerning the purpose of and basis for the proposed rule change and discussed any comments it received on the proposed rule change. The text of these statements may be examined at the places specified in Item IV below. The self-regulatory organization has prepared summaries, set forth in sections (A), (B) and (C) below, of the most significant aspects of such statements.

*A. Self-Regulatory Organization's Statement of the Purpose of, and Statutory Basis for, the Proposed Rule Change*

SCCP feels that it is appropriate that the fee schedule be published separately and referred to by, but not actually a part of, its rule relating to charges. This is the customary practice among clearing corporations.

The proposed reduction in the trading volume discount is being instituted in conjunction with a credit against PHILADEP charges in proportion to a participant's trading volume. This shift is being made in order that full SCCP/PHILADEP settling participants may receive some discount in PHILADEP charges as a result of their greater trading volume and revenues generated in supporting the SCCP/PHILADEP clearing and depository system.

The research fees are being instituted for the purpose of recovering SCCP's cost in providing copies to participants and in the time consumed in researching aged items at the request of participants.

The proposed rule change is consistent with the requirements of Section 17A(b)(3)(D) of the Securities Exchange Act of 1934 (the Act) in providing for the equitable allocation of reasonable dues, fees, and other charges among its participants.

*B. Self-Regulatory Organization's Statement on Burden on Competition*

SCCP does not perceive any impact on competition, negative or positive, resulting from the proposed rule change.

*C. Self-Regulatory Organization's Statement on Comments on the Proposed Rule Change*

Comments on the proposed rule change have been neither solicited nor received.

**III. Date of Effectiveness of the Proposed Rule Change and Timing for Commission Action**

The foregoing rule change has become effective pursuant to Section 19(b)(3) of the Securities Exchange Act of 1934 and subparagraph (e) of the Securities Exchange Act Rule 19b–4. At any time within 60 days of the filing of such proposed rule change, the Commission may summarily abrogate such rule change if it appears to the Commission that such action is necessary or appropriate in the public interest, for the protection of investors, or otherwise in furtherance of the purposes of the Securities Exchange Act of 1934.

**IV. Solicitation of Comments**

Interested persons are invited to submit written data, views and arguments concerning the foregoing. Persons making written submissions should file six copies thereof with the Secretary, Securities and Exchange Commission, 500 North Capitol Street, Washington, D.C. 20549. Copies of the submission, all subsequent amendments, all written statements with respect to the proposed rule change that are filed with the Commission, and all written communications relating to the proposed rule change between the Commission and any person, other than those that may be withheld from the public in accordance with the provisions of 5 U.S.C. 552, will be available for inspection and copying in the Commission's Public Reference Room, 1100 L Street, N.W., Washington, D.C. Copies of such filing will also be available for inspection and copying at the principal office of the above-mentioned self-regulatory organization. All submissions should refer to the file number in the caption above and should be submitted by June 16, 1982.

Dated: May 17, 1982.

For the Commission by the Division of Market Regulation, pursuant to delegated authority.

**Shirley E. Hollis,**

*Assistant Secretary.*

[FR Doc. 82-14194 Filed 5-24-82; 8:45 am]

BILLING CODE 8010-01-M

## SMALL BUSINESS ADMINISTRATION

### Small Business Investment Company; Maximum Annual Cost of Money to Small Business Concerns

13 CFR 107.301(c) sets forth the SBA Regulation governing the maximum annual cost of money to small business concerns for Financing by small business investment companies.

Section 107.301(c)(2) requires that SBA publish from time to time in the **Federal Register** the current Federal Financing Bank (FFB) rate for use in computing the maximum annual cost of money pursuant to § 107.301(c)(1). It is anticipated that a rate notice will be published each month.

13 CFR 107.301(c) does not supersede or preempt any applicable law that imposes an interest ceiling lower than the ceiling imposed by that regulation. Attention is directed to new subsection 308(i) of the Small Business Investment Act, added by section 524 of Pub. L. 96–221, March 31, 1980 (94 Stat. 161), to that law's Federal override of State usury ceilings, and to its forfeiture and penalty provisions.

Effective June 1, 1982, and until further notice, the FFB rate to be used for purposes of computing the maximum cost of money pursuant to 13 CFR Section 107.301(c) is 13.695% per annum.

Dated: May 19, 1982.

**Edwin T. Holloway,**

*Associate Administrator for Finance and Investment.*

[FR Doc. 82-14224 Filed 5-24-82; 8:45 am]

BILLING CODE 8025-01-M

## DEPARTMENT OF THE TREASURY

### Office of the Secretary

### Privacy Act of 1974; Systems of Records; Annual Publication

**AGENCY:** Department of the Treasury.

**SUMMARY:** The Privacy Act of 1974 (5 U.S.C. 552a(e)(4)) requires agencies to publish annually in the **Federal Register** a notice of the existence and character of their systems of records. The Department of the Treasury last published the full text of the Department's systems of records on page 16469, **Federal Register** Volume 46

dated March 12, 1981. The purpose of this document is to announce the updating of notices published on March 12, 1981 and to list systems deleted, consolidated, amended, or added since that time.

**DATES:** This document fulfills the annual notice requirement of the Privacy Act of 1974; (5 U.S.C. 552a(e)(4)).

**FOR FURTHER INFORMATION CONTACT:** Phillis De Piazza, Departmental Disclosure Officer, Department of the Treasury, Room 100, 1331 G, 1500 Pennsylvania Avenue, NW., Washington, D.C. 20220; Telephone (202) 376-1577.

**SUPPLEMENTARY INFORMATION:** The Department of the Treasury published its annual recompilation of system notices at 46 FR 16469, March 12, 1981. Notices concerning systems of records within the Department which were added or revised have been published in the **Federal Register** at 46 FR 6113, January 21, 1981 and 46 FR 57211, November 20, 1981. The Department has deleted 22 systems and consolidated 24 systems.

**Deletions**

*Office of the Secretary (OS)*
- OS 075—Legislative Affairs Vote Tracking System (System never implemented)
- OS 082—EEO Complaint Processing System (Maintained by EEOC)
- OS 101—International Criminal Police Organization (INTERPOL) Criminal Investigative Records (Maintained by the Justice Department, U.S. National Central Bureau)
- OS 102—Treasury Enforcement Communication System (TECS) (Same as OS 101)
- OS 141—Attorney Books (Obsolete)
- OS 157—Employee Records Cards (Duplicative)
- OS 400—Merit System Complaints (Obsolete)
- OS 503—Roster of Office of the Secretary Employees (Duplicative)
- OS 504—Summer Employees Listing (Duplicative)
- OS 505—Upward Mobility Program, Counseling Application (Obsolete)

*United States Customs Service (CS)*
- CS 245—Treasury Enforcement Communications System Card File (Obsolete)
- CS 016—Aircraft Ownership File (Not a Customs system. This is a Federal Aviation Agency system to which Customs has been granted access)
- CS 017—Aircraft Registers (Same as CS 016)

The following systems are covered under EEOC/Govt 1—Equal Employment Opportunity Complaint Records and Appeal Records.
- CS 060—Counseling Reports
- CS 088—Equal Opportunity Complaint Processing Records
- CS 089—Equal Opportunity Discrimination Complaint Case File
- CS 276—Equal Opportunity Informal Discrimination Complaint Files

*Bureau of Engraving & Printing (BEP)*
- BEP 008—Emergency Contact Records (Obsolete)
- BEP 025—Payroll Statistical Data (Duplicative)
- BEP 036—Union Dues Allotments (Duplicative)

*Internal Revenue Service (IRS)*
- IRS 32.004—Scholarship Program Cost Record (Obsolete)
- IRS 30.002—Employee Plans/Exempt Organization, Determination Letter Records (Not a Privacy Act System)

**Consolidations**

*Office of the Secretary (OS)*
- OS 142—Attorneys Past and Present (Covered under OS 152—General Counsel Personnel File)
- OS 148—Employment Application (Same as above)
- OS 153—Personnel: General Counsel, Deputy General Counsels and Assistant General Counsels (Same as above)

*United States Customs (CS)*
- CS 055—Congressional & Employment Correspondence (Covered under CS 056—Congressional and Public Correspondents File)
- CS 039—Carrier File (Covered under CS 040—Carrier File)
- CS 047—Claims Files (Region VIII) (Covered under CS 046—Claims Case File)
- CS 048—Claims for Automobile Accidents (Same as above)
- CS 266—Collection File (Same as above)
- CS 070—Customhouse Brokers, Headquarters Records (Covered under CS 069—Customhouse Brokers File, Chief Counsel)
- CS 071—Customhouse Brokers Records (Same as above)
- CS 102—Firearms Qualification Certificate Record (Covered under CS 103—Firearms Qualification Records)
- CS 142—Mail Entry Protest (Covered under CS 144—Mail Protest File)
- CS 143—Mail Protest (Same as above)
- CS 164—Overtime Earnings (Covered under CS 165—Overtime Earnings)
- CS 166—Overtime Earnings Daily Log Book (Same as above)
- CS 167—Overtime Earnings Records Customs Warehouse Officers (Same as above)
- CS 169—Overtime Log (Same as above)
- CS 171—Parking Permit File (NY Region) (Covered under CS 172—Parking Permits File)
- CS 187—Personal Search File (Covered under CS 186—Personal Search—Negative)
- CS 188—Personal Search File Report (Same as above)
- CS 221—Suspect File (Covered under CS 224—Suspect Persons Index)
- CS 240—Travel Advances (Covered under CS 243—Travel Payment System)
- CS 241—Travel Advances (Same as above)
- CS 242—Travel Advances File (Same as above)

*Internal Revenue Service (IRS)*
- IRS 42.025—Appraisal and Valuation Files (Covered under IRS. 42.001—Examination Administration File)
- IRS 42.018—Married Taxpayers Filing Separately and Mutiple Filer File (Same as above)
- IRS 42.023—Request and Submittal File for Technical Advice Assistance, Determination or Coordination (Same as above)
- IRS 80.004—Reference Index Digest Cards (Covered under IRS 80.003—Correpondence Control and Records)
- IRS 80.005—Reports of Significant Matters (Form M-5945) (Same as above)

**Additions**

*Office of the Secretary (OS)*
- OS 006—Building Passes

**Revisions**

*Office of the Secretary (OS)*
- OS 190—General Allegations and Investigative Records

**Availability of Compilation**

Members of the public may review all existing systems of records maintained by the Department of the Treasury by referring to:
- The March 12, 1981 annual publication found at 46 FR 16469;
- The additions and modifications found at the Federal Register citations set forth above; and
- The list of deleted and consolidated systems included in this notice.

Systems of records maintained by the Department of the Treasury are found in the latest compilation, "Privacy Act Issuances—1980 Compilation", at Volume II, page 552. The 1980 compilation is available from Regional Depository Libraries at 50 locations around the country and can be examined at these libraries free of charge. It is also available at the

General Services Administration Federal Information Centers, which are located at 30 central points around the country."Privacy Act Issuances—1981 Compilation" will be available at the same locations as above later this year.

Dated: May 14, 1982.

**Cora P. Beebe,**

*Assistant Secretary (Administration).*

[FR Doc. 82-14167 Filed 5-24-82; 8:45 am]

BILLING CODE 4810-25-M

## VETERANS ADMINISTRATION

### Advisory Committee on Former Prisoners of War; Meeting

The Veterans Administration gives notice under 38 U.S.C. 221 that a meeting of the Advisory Committee on Former Prisoners of War will be held in Room 304 at the Veterans Administration Central Office, 810 Vermont Avenue, NW., Washington, DC 20420, June 8 through 10, 1982. The purpose of the Committee is to consult with and advise the Administrator of Veterans' Affairs on the administration of benefits under title 38, United States Code, for veterans who are former prisoners of war and on the needs of such veterans with respect to compensation, health care, and rehabilitation.

The sessions will convene at 9 a.m. all days. These sessions will be open to the public up to the seating capacity of the room. Because this capacity is limited, it will be necessary for those wishing to attend to contact Miss Linda Gardner, Administrative Assistant to the Chief Benefits Director, Veterans Administration Central Office (phone 202/389-2455) prior to June 1, 1982.

Members of the public may direct questions or submit prepared statements for review by the Committee in advance of the meeting, in writing only, to Mr. H. B. Mars, Deputy Director, Compensation and Pension Service, Department of Veterans Benefits, Room 400, Veterans Administration Central Office. Submitted material must be received at least five days prior to the meeting. Such members of the public may be asked to clarify submitted material prior to consideration by the Committee. Summary minutes of the meeting and rosters of the Committee members may be obtained from Miss Linda Gardner at the aforementioned address.

Dated: May 19, 1982.

**Robert P. Nimmo,**

*Administrator.*

[FR Doc. 82-14192 Filed 5-24-82; 8:45 am]

BILLING CODE 6320-01-M

# Sunshine Act Meetings

Federal Register
Vol. 47, No. 101
Tuesday, May 25, 1982

This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

## CONTENTS



### 1

**COMMODITY CREDIT CORPORATION**

**"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT:** 47 FR 21675, May 19, 1982.

**PLACE:** Room 200-A, Administration Building, U.S. Department of Agriculture, Washington, D.C.

**STATUS:** Closed.

**MATTERS TO BE CONSIDERED:** Agenda will be announced when no longer sensitive since disclosure would reveal the information that the meeting was closed to protect; as set forth in 5 U.S.C. 552b(c)(9) (A) and (B) and 7 CFR 1409.6(b)(2)(ii).

**SUPPLEMENTARY INFORMATION:** The General Counsel certified this meeting may be closed. Five (5) members of the Board, as follows, voted to close this meeting:

1. John R. Block, Secretary of Agriculture. Chairman
2. Richard E. Lyng, Member
3. Seeley G. Lodwick, Member
4. William G. Lesher, Member
5. Everett G. Rank, Member

**CONTACT PERSON FOR MORE INFORMATION:** George E. Rippel, Acting Secretary, Commodity Credit Corporation, Post Office Box 2415, Room 5714-South Building, U.S. Department of Agriculture, Washington, D.C. 20013; Telephone (202) 447-4785.

[S-783-82 Filed 5-21-82; 1:11 pm]
BILLING CODE 3410-05-M

### 2

**CONSUMER PRODUCT SAFETY COMMISSION**

**TIME AND DATE:** 10:00 a.m., Thursday, May 27, 1982.

**LOCATION:** Third Floor Hearing Room, 1111—18th Street, N.W., Washington, D.C.

**STATUS:** Open to the Public.

**MATTERS TO BE CONSIDERED:**

1. *Election of Vice Chairman*
   The Commission will elect a Vice Chairman to serve from June 1, 1982 to May 31, 1983.
2. *CB Antennas*
   The staff will brief the Commission on issues related to issuance of a final consumer product safety standard for omnidirectional citizens band base station antennas.
3. *Physician Samples: Options*
   The staff will brief the Commission on issues related to the Commisson's policy regarding manufacturer's responsibility for special packaging of prescription drugs distributed to physicians.

For a recorded message on the lastest information concerning Commission agendas, call (301) 492-5709.

**CONTACT PERSON FOR ADDITIONAL INFORMATION:** Sheldon D. Butts, Deputy Secretary, Office of the Secretary, Suite 342, 5401 Westbard Avenue Bethesda, MD 20207; Telephone (301) 492-6800.

[S-786-82 Filed 5-21-82; 3:44 pm]
BILLING CODE 6355-01-M

### 3

**FEDERAL COMMUNICATIONS COMMISSION**

The Commission has scheduled an open meeting for May 27, at 10 a.m., in Room 856, 1919 M St. NW, to receive the final report of the Advisory Committee on Alternative Financing for Minority Opportunities in Telecommunications.

The Commission will also hold an open meeting to consider whether to issue a *Fourth Supplemental Notice of Inquiry and Proposed Rulemaking* in Docket 78-72 dealing with access charges in the Matter of MTS and WATS Market Structure at 2:00 p.m., in Room 856.

This meeting may be continued the following work day to allow the Commission to complete appropriate action.

Additional information concerning this meeting may be obtained from Maureen Peratino, FCC Public Affairs Office, telephone number (202) 254-7674.

Issued: May 20, 1982.

**William J. Tricarico,**
*Secretary, Federal Communications Commission.*

[S-784-82 Filed 5-21-82; 1:57 pm]
BILLING CODE 6712-01-M

### 4

**FEDERAL COMMUNICATIONS COMMISSION**

The Federal Communications Commission will consider an additional item on the subject listed below at the Open Meeting scheduled for 2:00 p.m., Thursday, May 27, 1982 at 1919 M Street, NW., Washington, D.C.

*Agenda, Item No., and Subject*

Complaints & Compliance—1—Democratic National Committee Fairness Doctrine complaint vs. CBS AND NBC.

This meeting may be continued the following work day to allow the Commission to complete appropriate action.

Additional information concerning this meeting may be obtained from Maureen Peratino, FCC Public Affairs Office, telephone number (202) 254-7674.

Issued: May 21, 1982.

**William J. Tricarico,**
*Secretary, Federal Communications Commission.*

[S-785-82 Filed 5-21-82; 1:57 pm]
BILLING CODE 6712-01-M

### 5

**NATIONAL TRANSPORTATION SAFETY BOARD**

**[NM-82-14]**

**TIME AND DATE:** 9 a.m., Tuesday, June 1, 1982.

**PLACE:** NTSB Board Room, National Transportation Safety Board, 800 Independence Avenue, S.W., Washington, D.C. 20594.

**STATUS:** The first item will be open to the public and the second item will be closed under Exemption 10 of the Government in the Sunshine Act.

**MATTERS TO BE CONSIDERED:**

1. *Aircraft Accident Report:* Eastern Airlines Flight 935, Lockheed L-1011-385, N309EA, near Colts Neck, New Jersey, September 22, 1981.
2. *Opinion and Order:* Petition of Parker, Dkt. SM-2828; disposition of the Administrator's appeal.

**CONTACT PERSON FOR MORE INFORMATION:** Sharon Flemming (202) 382-6525.

May 21, 1982.

[S-787-82 Filed 5-21-82; 3:56 pm]

BILLING CODE 4910-58-M

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**6**

**PAROLE COMMISSION**

**[2P0401]**

**TIME AND DATE:** 9 a.m.-5:30 p.m., Monday, June 21, 1982.

**PLACE:** Room 420-F, One North Park Building, 5550 Friendship Boulevard, Chevy Chase, Maryland 20815.

**STATUS:** Closed pursuant to a vote to be taken at the beginning of the meeting.

**MATTERS TO BE CONSIDERED:** Appeals to the Commission of approximately 10 cases decided by the National Commissioners pursuant to a reference under 28 CFR § 2.17 and appealed pursuant to 28 CFR § 2.27. These are all cases originally heard by examiner panels wherein inmates of Federal prisons have applied for parole or are contesting revocation of parole or mandatory release.

**CONTACT PERSON FOR MORE INFORMATION:** Linda Wines Marble, Chief Case Analyst, National Appeals Board, United States Parole Commission, (301) 492-5987.

[S-781-82 Filed 5-21-82; 11:08 am]

BILLING CODE 4410-01-M

federal register

Tuesday
May 25, 1982

Part II

# Department of Labor

## Employment Standards Administration

## Standards for Determining Coal Miner's Total Disability or Death Due to Pneumoconiosis; Claims for Benefits Under Part C of Title IV of the Federal Mine Safety and Health Act, as Amended

**DEPARTMENT OF LABOR**

**Employment Standards Administration**

**20 CFR Parts 718 and 725**

## Standards for Determining Coal Miner's Total Disability or Death Due to Pneumoconiosis; Claims for Benefits Under Part C of Title IV of the Federal Mine Safety and Health Act, as Amended

**AGENCY:** Employment Standards Administration, Labor.

**ACTION:** Notice of proposed rulemaking; request for comment.

**SUMMARY:** On January 1, 1982, the Black Lung Benefits Revenue Act of 1981 and the Black Lung Benefits Amendments of 1981 became effective. This legislation made numerous substantive changes in the Black Lung Benefits Act, Title IV of the Federal Mine Safety and Health Act. Those changes affect both the criteria for establishing eligibility for benefits on claims filed on and after January 1, 1982, under the Black Lung Benefits Act and the procedures for the payment of such benefits. These proposed rules are intended to implement those changes in the law and to make certain technical corrections in the implementing regulations previously promulgated in 1978 and 1980.

**DATE:** Written comments must be submitted on or before June 24, 1982.

**ADDRESS:** Send comments to James L. DeMarce, Executive Assistant to the Director, Office of Workers' Compensation Programs, Employment Standards Administration, Department of Labor, 200 Constitution Avenue, NW., Room S-3524, Washington, D.C. 20210; Telephone (202) 523-7503.

**FOR FURTHER INFORMATION CONTACT:** James L. DeMarce, Executive Assistant to the Director, Office of Workers' Compensation Programs, Employment Standards Administration, U.S. Department of Labor, 200 Constitution Avenue, NW., Room S-3524, Washington, D.C. 20210; Telephone (202) 523-7503.

**SUPPLEMENTARY INFORMATION:** The Black Lung Benefits Revenue Act of 1981 and the Black Lung Benefits Amendments of 1981, Pub. L. No. 97-119, 95 Stat. 1635, became effective on January 1, 1982. This legislation amended various sections of the Black Lung Benefits Act, Title IV of the Federal Mine Safety and Health Act of 1977, 30 U.S.C. 901 et seq., and the Internal Revenue Code, 26 U.S.C. 1 et seq. Those changes affect both the criteria for establishing eligibility for benefits on claims filed on and after January 1, 1982, under the Black Lung Benefits Act and the procedures for the payment of such benefits. Major changes include the removal of restrictions previously applicable to the Secretary of Labor's use of certain X-ray evidence and the placing of new limitations on the use of certain affidavits. Three presumptions previously available in support of claims have also been eliminated. (30 U.S.C. 921 (c)(2), (c)(4), and (c)(5)). Following the death of a miner whose claim was filed on or after January 1, 1982, and who was found to be entitled to benefits under the Act, the miner's dependent survivors will now be required to file a claim and to establish that the miner's death was due to pneumoconiosis in order to be found entitled to survivors' benefits under the Act. A new excess earnings offset was also made applicable, as were changes in the rates of interest to be paid to and by the Black Lung Disability Trust Fund and to claimants. The rate of the excise tax on coal was temporarily doubled and the liability for the payment of certain claims was transferred from individual coal mine operators and/or their insurance companies to the Fund. Certain other technical changes were also made by the amendments.

The primary purpose of these proposed rules is to amend the Department of Labor's implementing regulations which were previously published on August 18, 1978, 43 FR 36772, and February 29, 1980, 45 FR 13678, to conform to the Act, as now amended. A second purpose of the proposed rules is to make certain technical corrections in the regulations as previously promulgated. These corrections are intended to correct typographical and clerical errors, correct erroneous cross-references, and to make more uniform the language of certain provisions dealing with the same or similar subject matter. Other changes to the existing regulations which may be appropriate will be considered by the Department separately at a later date.

Sections 202 and 203 of the Black Lung Benefits Amendments of 1981 require the Department of Labor to undertake two studies and report the results, together with appropriate recommendations, to the Congress. Those studies are concerned with the medical diagnosis of pneumoconiosis, the impairment attributable to it, and the benefits available to persons who receive benefits under the Black Lung Benefits Act. It is not the intent of these proposed rules to anticipate the results of those studies or of any recommendations which may result from them. Comments concerning the subject matter of those studies should be addressed to: Willis Nordlund, Division of Evaluation and Research, Office of Program Development and Accountability, Employment Standards Administration, U.S. Department of Labor, 200 Constitution Avenue, N.W., Room S-3313, Washington, D.C. 20210; Telephone (202) 523-8493.

In developing these proposed rules, Department of Labor personnel have met with representatives of coal mining and consuming organizations, insurance groups, the United Mine Workers and black lung claimants' organizations. Informal comments and suggestions have been received from these groups which have been carefully considered and have been most helpful in the preparation of these proposed rules.

The Department particularly requests the submission of detailed formal comments on two areas of the draft regulations. The first concerns the definition of "death due to pneumoconiosis". See proposed rule § 718.205. Commenters are requested to focus upon the statements of Chairmen Hatch and Perkins contained in the Congressional Record for December 16, 1981, 127 Cong. Rec. at S15494 and H9792 (daily ed.). A second area where detailed comments are especially requested concerns the definition of the cases subject to the transfer of liability provisions.

See proposed rule § 725.496. Commenters are requested to provide detailed statements, including rationale and a listing of the points and authorities relied upon, in support of the positions taken concerning whether specific groups of cases are subject to the transfer of liability provisions.

### Drafting Information

This document was prepared under the direction and control of Robert B. Collyer, Deputy Under Secretary, Employment Standards Administration, U.S. Department of Labor, Room S-2321, 200 Constitution Avenue, N.W., Washington, D.C. 20210, Telephone (202) 523-6191.

### Classification—Executive Order 12291

The proposed rules only implement the 1981 amendments to the Black Lung Benefits Act and make certain technical corrections to the regulations as previously promulgated. They do not, in themselves, impose any additional requirements. Therefore, this proposal is not classified as a "major rule" under Executive Order 12291 on Federal Regulations, because it is not likely to result in (1) an annual effect on the economy of $100 million or more; (2) a

major increase in cost or prices for consumers, individual industries, Federal, State or local government agencies, or geographic regions; or (3) significant adverse effects on competition, employment, investment, productivity, innovation, or the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. Accordingly, no regulatory impact analysis is required.

**Paperwork Reduction Act**

The information collection requirements set forth in these rules as well as revised forms necessary to implement them are being submitted to OMB for its review and approved as required by the Paperwork Reduction Act.

**Regulatory Flexibility Act**

The Department believes that the rule will have no "significant economic impact upon a substantial number of small entities" within the meaning of section 3(a) of the Regulatory Flexibility Act. Pub. L. No. 96-354, 91 Stat. 1164 (5 U.S.C. 605(b)). The Secretary has certified to the Chief Counsel for Advocacy of the Small Business Administration to this effect. This conclusion is reached because the amendments are only implementing the 1981 amendments to the Black Lung Benefits Act and they do not, in themselves, impose any additional requirements upon small entities. Accordingly, no regulatory impact analysis is required.

**Regulatory Flexibility Act Certification**

I, Raymond J. Donovan, Secretary of Labor, hereby certify, pursuant to 5 U.S.C. 605(b), that the proposed rules contained in 20 CFR Parts 718 and 725, described in this document, will not have a significant economic impact on a substantial number of small entities. This conclusion is reached because the proposed rules only implement the 1981 amendments to the Black Lung Benefits Act and they do not, in themselves, impose any additional requirements upon small entities. Thus no economic impact is expected with respect to small entities.

Signed at Washington, D.C. this 21st day of May 1982.

Raymond J. Donovan,

*Secretary of Labor.*

The program affected by this rule and its program number in the Catalog of Federal Domestic Assistance is: Coal Mine Workers' Compensation (Black Lung), 17.307.

**List of Subjects in 20 CFR Part 718**

Black lung benefits, Lung diseases, Miners, Mines, Workers' compensation, X-rays.

**List of Subjects in 20 CFR Part 725**

Administrative practice and procedure, Black lung benefits, Lung diseases, Miners, Mines, Workers' compensation.

For the reasons set out in the preamble, Parts 718 and 725 of Chapter IV of Title 20 of the Code of Federal Regulations are proposed to be amended as follows:

## PART 718—STANDARDS FOR DETERMINING COAL MINER'S TOTAL DISABILITY OR DEATH DUE TO PNEUMOCONIOSIS

1. The authority for Part 718 reads as follows:

Authority: 5 U.S.C. 301, Reorganization Plan No. 6 of 1950, 15 FR 3174, 30 U.S.C. 901 et seq. 902(f), 925, 932, 934, 936, 945; 33 U.S.C. 901 et seq.

2. Section 718.1 is revised to read as follows:

**§ 718.1 Statutory provisions.**

(a) Under Title IV of the Federal Coal Mine Health and Safety Act of 1969, as amended by the Black Lung Benefits Act of 1972, the Federal Mine Safety and Health Amendments Act of 1977, the Black Lung Benefits Reform Act of 1977, the Black Lung Benefits Revenue Act of 1977, the Black Lung Benefits Amendments of 1981, and the Black Lung Benefits Revenue Act of 1981, benefits are provided to miners who are totally disabled due to pneumoconiosis and to certain survivors of a miner who died due to or while totally or partially disabled by pneumoconiosis. However, survivors' benefits are payable on claims filed on or after January 1, 1982, only when the miner's death was due to pneumoconiosis, except where the survivors' entitlement is established pursuant to § 718.306 of this part on a claim filed prior to June 30, 1982. Before the enactment of the Black Lung Benefits Reform Act of 1977, the authority for establishing standards of eligibility for miners and their survivors was placed with the Secretary of Health, Education, and Welfare. These standards were set forth by the Secretary of Health, Education, and Welfare in subpart D of part 410 of this title, and adopted by the Secretary of Labor for application to all claims filed with the Secretary of Labor (see 20 CFR 718.2, 1978). Amendments made to section 402(f) of the Act by the Black Lung Benefits Reform Act of 1977 authorize the Secretary of Labor to establish criteria for determining total or partial disability or death due to pneumoconiosis to be applied in the processing and adjudication of claims filed under Part C of Title IV of the Act. Section 402(f) of the Act further authorizes the Secretary of Labor, in consultation with the National Institute for Occupational Safety and Health, to establish criteria for all appropriate medical tests administered in connection with a claim for benefits. Section 413(b) of the Act authorizes the Secretary of Labor to establish criteria for the techniques to be used to take chest roentgenograms (X-rays) in connection with a claim for benefits under the Act.

(b) The Black Lung Benefits Reform Act of 1977 provided that with respect to a claim filed on or before the effective date of this part, that is, filed prior to April 1, 1980, or reviewed under section 435 of the Act, the standards to be applied in the adjudication of such claim shall not be more restrictive than the criteria applicable to a claim filed on June 30, 1973, with the Social Security Administration, whether or not the final disposition of the claim occurs after March 31, 1980. All such claims shall be reviewed under the criteria set forth in Part 727 of this title.

3. Section 718.2 is revised to read as follows:

**§ 718.2 Applicability of this part.**

This part is applicable to the adjudication of all claims filed after March 31, 1980, and considered by the Secretary of Labor under section 422 of the Act and Part 725 of this subchapter. If a claim subject to the provisions of section 435 of the Act and Subpart C of Part 727 of this subchapter cannot be approved under that subpart, such claim may be approved, if appropriate, under the provisions contained in this part. The provisions of this part shall, to the extent appropriate, be construed together in the adjudication of all claims.

4. In § 718.106, paragraph (b) is revised to read as follows:

**§ 718.106 Autopsy; biopsy.**

* * * * *

(b) No report of an autopsy or biopsy submitted in connection with a claim shall be considered unless the report complies with the requirements of this section. Special consideration shall, however, be given to the report of a biopsy or autopsy of a miner who died before March 31, 1980, even where the report is not in substantial compliance with the requirements of this section.

* * * * *

5. In § 718.202, paragraphs (a)(1)(i) and (c) are revised as follows:

**§ 718.202 Determining the existence of pneumoconiosis.**

(a) * * *

(1) * * *

(i) In all claims filed before January 1, 1982, where there is other evidence of pulmonary or respiratory impairment, a Board-certified or Board-eligible radiologist's interpretation of a chest X-ray shall be accepted by the office if the X-ray is in compliance with the requirements of § 718.102 and if such X-ray has been taken by a radiologist or qualified radiologic technologist or technician and there is no evidence that the claim has been fraudulently represented. However, these limitations shall not apply to any claim filed on or after January 1, 1982.

* * * * *

(c) A determination of the existence of pneumoconiosis shall not be made solely on the basis of a living miner's statements or testimony. Nor shall such a determination be made upon a claim involving a deceased miner filed on or after January 1, 1982, solely based upon the affidavit(s) of any person or persons having any financial interest in the result of the adjudication of the claim.

6. In § 718.204, paragraph (c)(5) is revised to read as follows:

**§ 718.204 Total disability defined. Criteria for determining total disability.**

* * * * *

(c) * * *

(5) In the case of a claim filed by the survivor of a miner, where there is no medical or other relevant evidence, the affidavits of persons knowledgeable of the miner's physical condition shall be sufficient to establish total disability. However, on such a surviror's claim filed on or after January 1, 1982, but prior to June 30, 1982, where entitlement is sought to be established in accordance with § 718.306, such a determination of the existence of total or partial disability shall not be based solely upon the affidavit(s) of any person or persons having any financial interest in the result of the adjudication of the claim.

* * * * *

7. Section 718.205 is amended by adding a new paragraph (c), revising former paragraph (c) and redesignating it as paragraph (d), and adding paragraph (e) to read as follows:

**§ 718.205 Death due to pneumoconiosis.**

* * * * *

(c) Neither the provisions of paragraph (b)(2) nor the presumptions referred to in paragraph (b)(4) are applicable to a survivor's claim filed on or after January 1, 1982.

(d) For the purpose of this section, death shall also be considered to be due to pneumoconiosis where the cause of death is significantly related to or aggravated by pneumoconiosis, or where pneumoconiosis was substantially contributing cause or factor leading to the miner's death or where the death was caused by complications of pneumoconiosis. For example, pneumoconiosis may have been a substantially contributing cause of death in a case where the principal cause of death was pneumonia. However, survivors are not eligible for benefits where the miner's death was caused by a traumatic injury or a medical condition not related to pneumoconiosis.

(e) Where the initial medical evidence establishes that death was due to pneumoconiosis as defined in this section, the survivor will receive benefits unless the weight of the evidence as subsequently developed by the Department or the responsible operator establishes that the miner's death was not due to pneumoconiosis as defined in this section. However, no such benefits shall be found payable before the party responsible for the payment of such benefits shall have had a reasonable opportunity for the development of rebuttal evidence.

8. Section 718.303 is amended by adding paragraph (c) to read as follows:

**§ 718.303 Death from a respirable disease.**

* * * * *

(c) This section is not applicable to any claim filed on or after January 1, 1982.

9. Section 718.305 is amended by adding paragraph (e) to read as follows:

**§ 718.305 Presumption of pneumoconiosis.**

* * * * *

(e) This section is not applicable to any claim filed on or after January 1, 1982.

10. In § 718.306, paragraph (a) is revised to read as follows:

**§ 718.306 Presumption of entitlement applicable to certain death claims.**

(a) In the case of a miner who died on or before March 1, 1978, who was employed for 25 or more years in one or more coal mines prior to June 30, 1971, the eligible survivors of such miner whose claims have been filed prior to June 30, 1982, shall be entitled to the payment of benefits, unless it is established that at the time of death such miner was not partially or totally disabled due to pneumoconiosis. Eligible survivors shall, upon request, furnish such evidence as is available with respect to the health of the miner at the time of death, and the nature and duration of the miner's coal mine employment.

* * * * *

## PART 725—CLAIMS FOR BENEFITS UNDER PART C OF TITLE IV OF THE FEDERAL MINE SAFETY AND HEALTH ACT, AS AMENDED

11. The authority for Part 725 reads as follows:

**Authority:** 5 U.S.C. 301, Reorganization Plan No. 6 of 1950, 15 FR 3174, 30 U.S.C. 901 et seq., 902(f), 925, 932, 934, 936, 945; 33 U.S.C. 901 et seq.

12. Section 725.1 is amended by revising paragraphs (a) and (g), redesignating paragraph (h) as paragraph (j) and adding new paragraphs (h) and (i) to read as follows:

**§ 725.1 Statutory provisions.**

(a) *General.* Title IV of the Federal Mine Safety and Health Act of 1977, as amended by the Black Lung Benefits Reform Act of 1977, the Black Lung Benefits Revenue Act of 1977, the Black Lung Benefits Revenue Act of 1981 and the Black Lung Benefits Amendments of 1981, provides for the payment of benefits to a coal mines who is totally disabled due to pneumoconiosis (black lung disease) and to certain survivors of a miner who dies due to pneumoconiosis. For claims filed prior to January 1, 1982, certain survivors could receive benefits if the miner was totally (or for claims filed prior to June 30, 1982, in accordance with section 411(c)(5) of the Act, partially) disabled due to pneumoconiosis, or who died due to pneumoconiosis.

* * * * *

(g) *Changes made by the Black Lung Benefits Revenue Act of 1977.* The Black Lung Benefits Revenue Act of 1977 established the Black Lung Disability Trust Fund which is financed by a specified tax imposed upon each ton of coal (except lignite) produced and sold or used in the United States after March 31, 1978. The Secretary of the Treasury is the managing trustee of the fund and benefits are paid from the fund upon the direction of the Secretary of Labor. The fund was made liable for the payment of all claims approved under section 415, Part C and section 435 of the Act for all periods of eligibility occurring on or after Janaury 1, 1974, with respect to claims where the miner's last coal mine employment terminated before January 1, 1970, or where individual liability can not be assessed against a coal mine operator due to bankruptcy, insolvency,

or the like. The fund was also authorized to pay certain claims which a responsible operator has refused to pay within a reasonable time, and to seek reimbursement from such operator. The purpose of the Fund and the Black Lung Benefits Revenue Act of 1977 was to insure that coal mine operators, or the coal industry, will fully bear the cost of black lung disease for the present time and in the future. The Black Lung Benefits Revenue Act of 1977 also contained other provisions relating to the fund and authorized a coal mine operator to establish its own trust fund for the payment of certain claims.

(h) *Changes made by the Black Lung Benefits Amendments of 1981.* In addition to the change reflected in paragraph (a) of this section, the Black Lung Benefits Amendments of 1981 made a number of significant changes in the Act's standards for determining eligibility for benefits and concerning the payment of such benefits. The following changes are all applicable to claims filed on or after January 1, 1982: (1) The Secretary of Labor may re-read any X-ray submitted in support of a claim and may rely upon a second opinion concerning such an X-ray as a means of auditing the validity of the claim; (2) the rebuttable presumption that the death of a miner with ten or more years employment in the coal mines, who died of a respirable disease, was due to pneumoconiosis is no longer applicable; (3) the rebuttable presumption that the total disability of a miner with fifteen or more years employment in the coal mines, who has demonstrated a totally disabling respiratory or pulmonary impairment, is due to pneumoconiosis is no longer applicable; (4) in the case of deceased miners, where no medical or other relevant evidence is available, only affidavits from persons having no financial interest in determining the results of the adjudication of the claim will be considered sufficient to establish entitlement to benefits; (5) following the death of a miner whose claim was filed on or after January 1, 1982, and who was found to be entitled to benefits under the Act, dependent survivors will be required to file a claim and to establish that the miner's death was due to pneumoconiosis in order to be found entitled to survivors' benefits under the Act; (6) benefits payable under this part are subject to an offset on account of excess earnings by the miner; and (7) other technical amendments.

(i) *Changes made by the Black Lung Benefits Revenue Act of 1981.* The Black Lung Benefits Revenue Act of 1981 temporarily doubles the amount of the tax upon coal until the Trust Fund shall have repaid all advances received from the United States Treasury and the interest on all such advances. The Fund is also made liable for the payment of certain claims previously denied under the 1972 version of the Act and subsequently approved under section 435 and for the reimbursement of operators and insurers for benefits previously paid by them on such claims. With respect to claims filed on or after January 1, 1982, the Fund's authorization for the payment of interim benefits is limited to the payment of prospective benefits only. These changes also define the rates of interest to be paid to and by the Fund.

(j) *Longshoremen's Act provisions.* The adjudication of claims filed under sections 415, 422 and 435 of the Act is governed by various procedural and other provisions contained in the Longshoremen's and Harbor Workers' Compensation Act (LHWCA), as amended from time to time, which are incorporated within the Act by sections 415 and 422. The incorporated LHWCA provisions are applicable under the Act except as is otherwise provided by the Act or as provided by regulations of the Secretary. Although occupational disease benefits are also payable under the LHWCA, the primary focus of the procedures set forth in that Act is upon a time definite of traumatic injury or death. Because of this and other significant differences between a black lung and longshore claim, it is determined, in accordance with the authority set forth in section 422 of the Act, that certain of the incorporated procedures prescribed by the LHWCA must be altered to fit the circumstances ordinarily confronted in the adjudication of a black lung claim. The changes made are based upon the Department's experience in processing black lung claims since July 1, 1973, and all such changes are specified in this part or part 727 of this subchapter. No other departure from the incorporated provisions of the LHWCA is intended.

13. Section 725.4 is amended by revising paragraphs (a) and (d) to read as follows:

**§ 725.4 Applicability of other parts in this title.**

(a) *Part 718.* Part 718 of this subchapter, which contains the criteria and standards to be applied in determining whether a miner is or was totally disabled due to pneumoconiosis, or whether a miner died due to pneumoconiosis, shall be applicable to the determination of claims under this part. Claims filed after March 31, 1980, are subject to the revised part 718 as promulgated by the Secretary in accordance with section 402(f)(1) of the Act on February 29, 1980. The criteria contained in subpart C of part 727 of this sub-chapter are applicable in determining claims filed prior to April 1, 1980, under this part, and such criteria shall be applicable at all times with respect to claims filed under this part and under section 11 of the Black Lung Benefits Reform Act of 1977.

* * * * *

(d) *Part 727.* Part 727 of this subchapter, which governs the review, adjudication and payment of pending and denied claims under section 435 of the Act, is applicable to this part as provided in such part 727. The criteria contained in subpart C of part 727 for determining a claimant's eligibility for benefits shall be applicable under this part with respect to all claims filed before April 1, 1980, and to all claims filed under this part and under section 11 of the Black Lung Benefits Reform Act of 1977.

* * * * *

14. Section 725.101 is amended by revising paragraphs (a)(1) and (a)(31) and revising paragraph (a)(10) to read as follows:

**§ 725.101 Definitions and use of terms.**

(a) * * *

(1) The "Act" means the Federal Coal Mine Health and Safety Act, Pub. L. 91-173, 83 Stat. 742, 30 U.S.C. 801-960, as amended by the Black Lung Benefits Act of 1972, the Mine Safety and Health Act of 1977, the Black Lung Benefits Reform Act of 1977, the Black Lung Benefits Revenue Act of 1977, the Black Lung Benefits Revenue Act of 1981, and the Black Lung Benefits Amendments of 1981.

* * * * *

(10) "Division" or "DCMWC" means the Division of Coal Mine Workers' Compensation in the OWCP, United States Department of Labor.

* * * * *

(31) "Black Lung Disability Trust Fund" or the "Fund" means the Black Lung Disability Trust Fund established by the Black Lung Benefits Revenue Act of 1977, as amended by the Black Lung Benefits Revenue Act of 1981, for the payment of certain claims adjudicated under this part (see subpart G of this part).

* * * * *

15. In § 725.102, paragraph (a) is revised to read as follows:

**§ 725.102 Disclosure of program information.**

(a) All reports, records, or other documents filed with the OWCP with respect to claims are the records of the OWCP. The Director or his or her designee shall be the official custodian of those records maintained by the OWCP at its national office. The Deputy Commissioner shall be the official custodian of those records maintained at a district office.

* * * * *

16. Section 725.201 is amended by revising paragraphs (a)(2), (a)(4), and (b) to read as follows:

**§ 725.201 Who is entitled to benefits; contents of this subpart.**

(a) * * *

(2) The surviving spouse or surviving divorced spouse or, where neither exists, the child of a deceased miner, where the deceased miner;

(i) Was receiving benefits under section 415 or Part C of title IV of the Act as a result of a claim filed prior to January 1, 1982; or

(ii) Is determined as a result of a claim filed prior to January 1, 1982, to have been totally disabled due to pneumoconiosis at the time of death, or to have died due to pneumoconiosis. Survivors of miners whose claims are filed on or after January 1, 1982, must establish that the deceased miner's death was due to pneumoconiosis in order to establish their entitlement to benefits, except where entitlement is established under § 718.306 of part 718 on a survivor's claim filed prior to June 30, 1982, or;

* * * * *

(4) The surviving dependent parents, where there is no surviving spouse or child, or the surviving dependent brothers or sisters, where there is no surviving spouse, child, or parent, of a miner, where the deceased miner;

(i) Was receiving benefits under section 415 or Part C of title IV of the Act as a result of a claim filed prior to January 1, 1982; or

(ii) Is determined as a result of a claim filed prior to January 1, 1982, to have been totally disabled due to pneumoconiosis at the time of death, or to have died due to pneumoconiosis. Survivors of minors whose claims are filed on or after January 1, 1982, must establish that the deceased miner's death was due to pneumoconiosis in order to establish their entitlement to benefits, except where entitlement is established under § 718.306 of part 718 on a survivor's claim filed prior to June 30, 1982.

(b) Section 411(c)(5) of the Act provides for the payment of benefits to the eligible survivors of a miner employed for 25 or more years in the mines prior to June 30, 1971, if the miner's death occurred on or before March 1, 1978, and if the claim was filed prior to June 30, 1982, unless it is established that at the time of death, the miner was not totally or partially disabled due to pneumoconiosis. For the purposes of this part the term "total disability" shall mean partial disability with respect to a claim for which eligibility is established under section 411(c)(5) of the Act. See § 718.306 of part 718 which implements this provision of the Act.

* * * * *

17. Section 725.205 is amended by revising paragraph (c) as follows:

**§ 725.205 Determination of dependency; spouse.**

* * * * *

(c) The miner has been ordered by a court to contribute to such individual's support (see § 725.233(e)); or

* * * * *

18. Section 725.207 is amended by revising paragraph (c) to read as follows:

**§ 725.207 Determination of dependency; divorced spouse.**

* * * * *

(c) A court order requires the miner to furnish substantial contributions to the individual's support (see § 725.233 (c), (e)).

19. Section 725.208 is amended by revising paragraphs (f)(1) and (f)(2) to read as follows:

**§ 725.208 Determination of relationship; child.**

* * * * *

(f) * * *

(1) The beneficiary, prior to his or her entitlement to benefits, has acknowledged in writing that the individual is his or her son or daughter, or has been decreed by a court to be the parent of the individual, or has been ordered by a court to contribute to the support of the individual (see § 725.233(e)) because the individual is his or her son or daughter; or

(2) Such beneficiary is shown by satisfactory evidence to be the father or mother of the individual and was living with or contributing to the support of the individual at the time the beneficiary became entitled to benefits.

20. Section 725.212 is revised to read as follows:

**§ 725.212 Condition of entitlement; surviving spouse or surviving divorced spouse.**

(a) An individual who is the surviving spouse or surviving divorced spouse of a miner is eligible for benefits if such individual:

(1) Is not married;

(2) Was dependent on the miner at the pertinent time; and

(3) The deceased miner either:

(i) Was receiving benefits under section 415 or part C of title IV of the Act at the time of death as a result of a claim filed prior to January 1, 1982; or

(ii) Is determined as a result of a claim filed prior to January 1, 1982, to have been totally disabled due to pneumoconiosis at the time of death or to have died due to pneumoconiosis. A surviving spouse or surviving divorced spouse of a miner whose claim is filed on or after January 1, 1982, must establish that the deceased miner's death was due to pneumoconiosis in order to estabish entitlement to benefits, except where entitlement is established under § 718.306 of part 718 on a claim filed prior to June 30, 1982.

21. Section 725.213 is amended by revising paragraph (b)(3) to read as follows:

**§ 725.213 Duration of entitlement; surviving spouse or surviving divorced spouse.**

* * * * *

(b) * * *

(3) Where the individual qualifies as the surviving spouse of a miner under § 725.204(d), such individual ceases to qualify as provided in that paragraph.

22. Section 725.214 is amended by revising paragraph (d) to read as follows:

**§ 725.214 Determination of relationship; surviving spouse.**

* * * * *

(d) Such individual went through a marriage ceremony with the miner resulting in a purported marriage between them and which but for a legal impediment (see § 725.230) would have been a valid marriage, unless such individual entered into the purported marriage with knowledge that it was not a valid marriage, or if such individual and the miner were not living in the same household at the time of the miner's death. The provisions of this paragraph shall not apply if another person is or has been entitled to benefits as the surviving spouse of the miner and such other person is, or is considered to be, the surviving spouse of such miner under paragraph (a), (b), or (c) of this section at the time such individual files a claim for benefits.

23. Section 725.217 is amended by revising paragraphs (a)(1), (a)(2) and (a)(3) to read as follows:

**§ 725.217 Determination of dependency; surviving divorced spouse.**

(a) * * *

(1) The individual was receiving at least one-half of his or her support from the miner (see § 725.233(g)); or

(2) The individual was receiving substantial contributions from the miner pursuant to a written agreement (see § 725.233 (e) and (f)); or

(3) A court order required the miner to furnish substantial contributions to the individual's support (see § 725.233(c) and (e)).

24. Section 725.218 is amended by revising paragraphs (a)(1) and (a)(2) to read as follows:

**§ 725.218 Conditions of entitlement; child.**

(a) * * *

(1) Was receiving benefits under section 415 or Part C of title IV of the Act as a result of a claim filed prior to January 1, 1982; or

(2) Is determined as a result of a claim filed prior to January 1, 1982, to have been totally disabled due to pneumoconiosis at the time of death, or to have died due to pneumoconiosis. A surviving dependent child of a miner whose claim is filed on or after January 1, 1982, must establish that the miner's death was due to pneumoconiosis in order to establish entitlement to benefits, except where entitlement is established under § 718.306 of part 718 on a claim filed prior to June 30, 1982.

* * * * *

25. Section 725.219 is amended by revising paragraph (b)(3)(ii) to read as follows:

**§ 725.219 Duration of entitlement; child.**

* * * * *

(b) * * *

(3) * * *

(ii) Is not a student (as defined in § 725.209(d)) during any part of the month in which the child attains age 18;

* * * * *

26. Section 725.220 is amended by revising paragraph (f)(2) to read as follows:

**§ 725.220 Determination of relationship; child.**

* * * * *

(f) * * *

(2) Such beneficiary is shown by satisfactory evidence to be the father or mother of the individual and was living with or contributing to the support of the individual at the time such beneficiary became entitled to benefits.

27. Section 725.222 is amended by revising paragraphs (a)(5)(i) and (a)(5)(ii) to read as follows:

**§ 725.222 Conditions of entitlement; parent, brother, or sister.**

(a) * * *

(5) * * *

(i) Was entitled to benefits under section 415 or Part C of title IV of the Act as a result of a claim filed prior to January 1, 1982; or

(ii) Is determined as a result of a claim filed prior to January 1, 1982, to have been totally disabled due to pneumoconiosis at the time of death or to have died due to pneumoconiosis. A surviving dependent parent, brother or sister of a miner whose claim is filed on or after January 1, 1982, must establish that the miner's death was due to pneumoconiosis in order to establish entitlement to benefits, except where entitlement is established under § 718.306 of part 718 on a claim filed prior to June 30, 1982.

* * * * *

28. Section 725.225 is amended by revising paragraph (b) to read as follows:

**§ 725.225 Determination of dependency; parent, brother, or sister.**

* * * * *

(b) The individual was totally dependent on the miner for support (see § 725.233(h)).

29. Section 725.367 is amended by redesignating the existing text as paragraph (a) and adding paragraph (b). As amended § 725.367 reads as follows:

**§ 725.367 Payment of a claimant's attorney's fee by responsible operator.**

(a) If an operator declines to pay any benefits on or before the 30th day after receiving written notice of its liability for a claim on the ground that there is no liability for benefits within the provisions of the Act, and the person seeking benefits shall thereafter have utilized the services of an attorney in the successful prosecution of the claim, there shall be awarded, in addition to the award of benefits, in an order, a reasonable attorney's fee against the operator or carrier in an amount approved by the deputy commissioner, administrative law judge, Board, or court as the case may be, which shall be paid promptly and directly by the operator or carrier to the claimant's attorney in a lump sum after the order becomes final.

(b) Section 205(a) of the Black Lung Benefits Amendments of 1981, Pub. L. No. 97–119, amended section 422 of the Act and relieved operators and carriers from liability for the payment of benefits on certain claims. Payment of benefits on those claims was made the responsibility of the Trust Fund. The claims subject to this transfer of liability are described in § 725.496 of this part. On claims subject to the transfer of liability described above the Trust Fund will pay all fees and costs which have been or will be awarded to claimant's attorneys which were or would have become the liability of an operator or carrier but for the enactment of the 1981 Amendments and which have not already been paid by such operator or carrier. Section 9501(d)(7) of the Internal Revenue Code, which was also enacted as a part of the 1981 Amendments to the Act, expressly prohibits the Trust Fund from reimbursing an operator or carrier for any attorney fees or costs which it has paid on cases subject to the transfer of liability provisions.

30. Section 725.420 is amended by revising paragraph (a) and revising paragraph (b) to read as follows:

**§ 725.420 Initial determinations.**

(a) Section 9501(d)(1)(A)(1) of the Internal Revenue Code provides that the Black Lung Disability Trust Fund shall begin the payment of benefits on behalf of an operator in any case in which the operator liable for such payments "has not commenced payment of such benefits within 30 days after the date of an initial determination of eligibility by the Secretary * * *." For claims filed on or after January 1, 1982, the payment of such interim benefits from the Fund is limited to "benefits accruing after the date of such initial determination * * *."

(b) Except as provided in § 725.415 of this subpart, after the deputy commissioner has determined that a claimant is eligible for benefits, on the basis of all evidence submitted by a claimant and operator, and has determined that a hearing will be necessary to resolve the claim, the deputy commissioner shall in writing so inform the parties and direct the operator to begin the payment of benefits to the claimant in accordance with § 725.522. The date on which this writing is sent to the parties shall be considered the date of initial determination of the claim.

* * * * *

31. In § 725.421, paragraph (b)(1) is revised to read as follows:

**§ 725.421 Referral of a claim to the Office of Administrative Law Judges.**

* * * * *

(b) * * *

(1) Copies of the claim form or forms;

* * * * *

32. In § 725.456, paragraph (b)(1) is revised to read as follows:

**§ 725.456 Introduction of documentary evidence.**

* * * * *

(b)(1) Any other documentary material, including medical reports, which was not submitted to the deputy commissioner, may be received in evidence subject to the objection of any party, if such evidence is sent to all other parties at least 20 days before a hearing is held in connection with the claim.

* * * * *

33. In § 725.490, paragraph (a) is revised to read as follows:

**§ 725.490 Statutory provisions and scope.**

(a) One of the major purposes of the black lung benefits amendments of 1977 was to provide a more effective means of transferring the responsibility for the payment of benefits from the Federal government to the coal industry with respect to claims filed under this part. In furtherance of this goal, a Black Lung Disability Trust Fund financed by the coal industry was established by the Black Lung Benefits Revenue Act of 1977. The primary purpose of the Fund is to pay benefits with respect to all claims in which the last coal mine employment of the miner on whose account the claim was filed occurred before January 1, 1970. With respect to most claims in which the miner's last coal mine employment occurred after January 1, 1970, individual coal mine operators will be liable for the payment of benefits. The 1981 amendments to the Act relieved individual coal mine operators from the liability for payment of certain special claims involving coal mine employment on or after January 1, 1970, where the claim was previously denied and subsequently approved under section 435 of the Act. See § 725.496 for a detailed description of these special claims. Where no such operator exists or the operator determined to be liable is in default in any case, the Fund shall pay the benefits due and seek reimbursement as is appropriate. See also § 725.420 for the Fund's role in the payment of interim benefits in certain contested cases. In addition, the Black Lung Benefits Reform Act of 1977 amended certain provisions affecting the scope of coverage under the Act and describing the effects of particular corporate transactions on the liability of operators.

* * * * *

34. Section 725.496 is added to part 725 to read as follows:

**§ 725.496 Special claims transferred to the Trust Fund.**

(a) The 1981 amendments to the Act amended section 422 of the Act and transferred liability for payment of certain special claims from operators and carriers to the Trust Fund. These provisions apply to claims which were denied before March 1, 1978, and which have been or will be approved in accordance with section 435 of the Act.

(b) Section 402(i) of the Act defines three classes of denied claims subject to the transfer provisions:

(1) Claims filed with and denied by the Social Security Administration before March 1, 1978;

(2) Claims filed with the Department of Labor in which the claimant was notified by the Department of an administrative or informal denial before March 1, 1977, and in which the claimant did not within one year of such notification either:

(i) Request a hearing; or

(ii) Present additional evidence; or

(iii) Indicate an intention to present additional evidence;

(3) Claims filed with the Department of Labor and denied under the law in effect prior to the enactment of the Black Lung Benefits Reform Act of 1977, that is, before March 1, 1978, following a formal hearing before an administrative law judge or administrative review before the Benefits Review Board or review before a United States Court of Appeals.

(c) Where more than one claim was filed with the Social Security Administration and/or the Department of Labor prior to March 1, 1978, by or on behalf of a miner or a surviving dependent of a miner, unless such claims were merged in accordance with the agency's regulations, the procedural history of each such claim must be considered separately to determine whether the claim is subject to the transfer of liability provisions.

(d) For a claim filed with and denied by the Social Security Administration prior to March 1, 1978, to come within the transfer provisions, such claim must have been or must be approved under the provisions of section 435 of the Act. No claim filed with and denied by the Social Security Administration is subject to the transfer of liability provisions unless a request was made by or on behalf of the claimant for review of such denied claim under section 435. Such review must have been requested by the filing of a valid election card or other equivalent document with the Social Security Administration in accordance with section 435(a).

(e) Where a claim filed with the Department of Labor prior to March 1, 1977, was subjected to repeated administrative or informal denials, the last such denial issued during the pendency of the claim determines whether the claim is subject to the transfer of liability provisions.

(f) Where a miner's claim comes within the transfer of liability provisions of the 1981 amendments the Trust Fund is also liable for the payment of any benefits to which the miner's dependent survivors are entitled after the miner's death. However, if the survivor's entitlement was established on a separate claim not subject to the transfer of liability provisions prior to approval of the miner's claim under section 435, the party responsible for the payment of such survivors' benefits shall not be relieved of that responsibility because the miner's claim was ultimately approved and found subject to the transfer of liability provisions.

35. In § 725.520, the introductory text of paragraph (a), paragraphs (a)(1), (a)(2), and (a)(3) are revised and paragraph (a)(4) is removed to read as follows:

**§ 725.520 Computation of benefits.**

(a) *Basic rate.* The amount of benefits payable to a beneficiary for a month is determined, in the first instance, by computing the "basic rate." The basic rate is equal to 37½ percent of the monthly pay rate for Federal employees in GS–2, step 1. That rate for a month is determined by:

(1) Ascertaining the lowest annual rate of pay (step 1) for Grade GS–2 of the General Schedule applicable to such month (see 5 U.S.C. 5332);

(2) Ascertaining the monthly rate thereof by dividing the amount determined in paragraph (a)(1) of this section by 12; and

(3) Ascertaining the basic rate under the Act by multiplying the amount determined in paragraph (a)(2) of this section by 0.375 (that is, by 37½ percent).

* * * * *

36. In § 725.532, paragraph (a) is revised to read as follows:

**§ 725.532 Suspension, reduction, or termination of payments.**

(a) No suspension, reduction, or termination in the payment of benefits is permitted unless authorized by the deputy commissioner, administrative law judge, Board, or court. No suspension, reduction or termination shall be authorized except upon the occurrence of an event which terminates a claimant's eligibility for benefits (see subpart B of this part) or as is otherwise provided in subpart C of this part, §§ 725.306 and 725.310, or this subpart (see also §§ 725.533–725.546).

* * * * *

37. In § 725.533, paragraph (a)(3) is revised to read as follows:

**§ 725.533 Modification of benefit amounts; general.**

(a) * * *

(3) In the case of benefits payable to a parent, brother, or sister as a result of a claim filed at any time or benefits payable on a miner's claim which was filed on or after January 1, 1982, the excess earnings from wages and from net earnings from self-employment (see § 410.530 of this title) of such parent, brother, sister, or miner, respectively; or

* * * * *

38. Section 725.536 is revised to read as follows:

**§ 725.536 Reductions; excess earnings.**

In the case of a surviving parent, brother, or sister, whose claim was filed at any time, or of a miner whose claim was filed on or after January 1, 1982, benefit payments are reduced as appropriate by an amount equal to the deduction which would be made with respect to excess earnings under the provisions of sections 203 (b), (f), (g), (h), (j), and (l) of the Social Security Act (42 U.S.C. 403 (b), (f), (g), (h), (j), and (l)), as if such benefit payments were benefits payable under section 202 of the Social Security Act (42 U.S.C. 402) (see §§ 404.428–404.456 of this title).

39. Section 725.608 is amended by revising paragraphs (a) and (b), redesignating previous paragraph (c) as paragraph (d), and adding a new paragraph (c) to read as follows:

**§ 725.608 Interest.**

(a) If an operator or other employer fails or refuses to pay any or all benefits due under the terms of an initial determination by a deputy commissioner (§ 725.420), a decision and order filed and served by an administrative law judge (§ 725.478) or a decision filed by the Board or a United States court of appeals, including any penalty awarded in addition to benefits in accordance with § 725.607, such operator shall be liable for simple annual interest on all past due benefits computed from the date on which such benefits were due and payable, in addition to such operator's or other employer's liability as is otherwise provided in this part. On claims filed on or after January 1, 1982, in which the payment of retroactive benefits has been withheld pending final adjudication of liability in accordance with section 422(d) of the Act as amended, interest on such withheld retroactive benefit payments shall begin to accumulate 30 days after the date of the first determination that such an award should be made. The first determination that such an award should be made may be a deputy commissioner's initial determination of entitlement, an award made by an administrative law judge or a decision issued by the Board or a court, whichever is the first such determination of entitlement made upon the claim. Except as provided in paragraph (b) of this section, interest payments owed under this paragraph shall be made directly to the beneficiary.

(b) If an operator or other employer fails or refuses to pay any or all benefits due pursuant to an award of benefits or an initial determination of eligibility made by the deputy commissioner and the Fund undertakes such payments, such operator or other employer shall be liable to the Fund for simple annual interest on all payments made by the Fund for which such operator is determined liable, computed from the first date on which such benefits are paid by the Fund, in addition to such operator's liability to the Fund, as is otherwise provided in this part. Interest payments owed pursuant to this paragraph shall be paid directly to the Fund.

(c) The rates of interest applicable to paragraphs (a) and (b) above shall be computed as follows:

(1) For all amounts outstanding prior to January 1, 1982, the rate shall be 6% simple annual interest,

(2) For all amounts outstanding for any period during calendar year 1982 the rate shall be 15% simple annual interest; and

(3) For all amounts outstanding during any period after calendar year 1982 the rate shall be simple annual interest at the rate established by section 6621 of the Internal Revenue Code of 1954 which is in effect for such period.

(d) The Fund shall not be liable for the payment of interest under any circumstances.

Signed at Washington, D.C. this 21st day of May 1982.

**Raymond J. Donovan,**

*Secretary of Labor.*

[FR Doc. 82-14285 Filed 5-24-82; 8:45 am]

BILLING CODE 4510-27-M

federal register

Tuesday
May 25, 1982

Part III

# Department of Agriculture

## Food and Nutrition Service

## Food Stamp Program; Monthly Reporting and Retrospective Budgeting

**DEPARTMENT OF AGRICULTURE**

**Food and Nutrition Service**

**7 CFR Parts 271, 272, and 273**

**[Amdt. No. 184]**

## Food Stamp Program: Monthly Reporting and Retrospective Budgeting

**AGENCY:** Food and Nutrition Service, USDA.

**ACTION:** Interim rule.

**SUMMARY:** This interim final rule permits State agencies to compute food stamp benefits for most recipients by using past information about them, rather than anticipated future circumstances. The rule also permits State agencies to require most food stamp recipients to report periodically their financial circumstances to the State agencies. After October 1, 1983, State agencies will be required to use these procedures in calculating household income for most households. The Food Stamp Act of 1977 (7 U.S.C. 2011, *et seq.*), as amended, authorizes the Food Stamp Program to make these changes.

**DATES:** Interim rule effective May 25, 1982; comments must be received on or before September 22, 1982 to be assured of consideration.

**ADDRESS:** Please submit comments to Thomas O'Connor, Supervisor, Policy and Regulations Section, Family Nutrition Programs, Food and Nutrition Service, USDA, Alexandria, Virginia 22302: (703) 756–3429. Comments will be available for public inspection during regular business hours (8:30 a.m. to 5:00 p.m.) at the agency's offices: Room 708, 3101 Park Center Drive, Alexandria, Virginia.

**FOR FURTHER INFORMATION CONTACT:** Mr. Thomas O'Connor (703) 756–3429 at the mailing address listed above. Copies of the preliminary Regulatory Impact Analysis, which is summarized in this preamble, are also available to the public from Mr. O'Connor.

**SUPPLEMENTARY INFORMATION:**

### Publication

The Department is making this rule effective upon publication because of its close relationship to a rule published by the Department of Health and Human Services (HHS) on February 5, 1982 (47 FR 5648). The HHS rule establishes a Monthly Reporting and Retrospective Budgeting system (MRRB) for the Aid to Families with Dependent Children (AFDC) Program and was to have been implemented on October 1, 1981. Some States are currently designing and preparing to implement a system for both the AFDC and the Food Stamp Program and an early effective date for this rule will expedite that process. The Department previously published a proposed rule and received public comments on many of the issues addressed in this rule.

In accordance with the Paperwork Reduction Act of 1980 (44 U.S.C. 3507), the reporting and recordkeeping requirements contained in this regulation have been approved by the Office of Management and Budget (OMB). (OMB approval No. 0584–0064).

### Regulatory Flexibility Act

The Administrator of the Food and Nutrition Service has certified that this action will not have a significant economic impact on a substantial number of small entities. This action will mainly affect Food Stamp Program applicants and recipients, and the State and local agencies which administer the Program. Some of these agencies may automate their administrative procedures as a direct result of this rule. However, the rule does not require automation of these procedures and such automation will not significantly affect small business.

### Executive Order 12291

Pursuant to section 4(c) of Executive Order 12291, the Department has determined that this rule is within the authority delegated by law. The Secretary has further determined that this rule is necessary to implement statutory changes and to improve the efficiency of the Food Stamp Program. The Department considers this rule a major rule. All State agencies are required to implement this rule by fiscal year 1984. In that year, it is estimated that this rule will reduce the Food Stamp Program's cost by about $280 million if State agencies maintain these procedures when administration of the Program passes to them. Because this is a major rule, the Department has prepared a preliminary Regulatory Impact Analysis.

### Interim Rule

In the Food Stamp Act Amendments of 1980 (Pub. L. 96–249, 94 Stat. 357, May 26, 1980, referred to herein as the 1980 amendments), Congress permitted State agencies to use retrospective budgeting and periodic reporting in operating the Food Stamp Program. The Department published a proposed rule on December 5, 1980 (45 FR 80790), which would have authorized this optional system. The Department received 68 comment letters on retrospective budgeting and monthly reporting. The commenters included State and local welfare agencies, recipient groups, churches and legal assistance organizations. Before a final regulation could be issued the Congress enacted the Omnibus Budget Reconciliation Act of 1981 (Pub. L. 97–35, 95 Stat. 358, August 13, 1981 referred to herein as the Reconciliation Act) which altered some features of the system.

The Reconciliation Act made a few specific and precise changes regarding the retrospective accounting (section 5(f)) and the periodic reporting (section 6(c)) provisions of the Food Stamp Act of 1977, as amended by the 1980 amendments. However, the Reconciliation Act did not alter the fundamental concepts of retrospective accounting and periodic reporting as established by the 1980 Amendments. The comment letters received regarding the December 5, 1980 proposal on retrospective accounting and periodic reporting (but based on the 1980 Amendments) provided useful information in these topics. In addition to the sixty-eight comment letters, a number of which were very detailed, FNS held an open meeting on retrospective accounting and periodic reporting which was attended by representatives of twenty-nine groups. Vermont noted that "the meeting on Jaunuary 13th was very helpful because it was a working session which facilitated the exchange of ideas and experience between States and the Food and Nutrition Service." This interim rulemaking is thus based on the extensive written and oral comments described above and on the statutory changes contained in the Reconciliation Act.

The Department is convinced that the public interest would not be served by delaying implementation of specific changes in the Reconciliation Act until public comment is received regarding topics already thoroughly addressed in public comment. Nonetheless, to maximize opportunity for public input the Department invites comment on these interim rules. The Department hopes to obtain comments based upon the actual experience of States and food stamp recipients with these interim rules. Those comments should prove more useful than another set of comments based on a second proposal. The Department has additionally determined to make this rule effective on publication to allow States to integrate their AFDC operation with their food stamp systems.

**Reconciliation Act Changes Regarding the 1980 Amendments**

Persons wishing to comment on this interim rule should be aware of the specific requirements imposed by statute since those provisions cannot be altered through the rulemaking process. To avoid confusion the precise changes made by the Reconciliation Act are described. As mentioned earlier, the Food Stamp Act as amended by the Reconciliation Act and as earlier amended by the 1980 Amendments defined prospective accounting and retrospective accounting in very similar fashions. The essential differences center on those types of households for which exceptions or modifications in retropsective accounting and periodic reporting could be made.

The 1980 Amendments required the Department to modify the retrospective accounting rules (imposed by the 1980 Amendments) for three specific classes of households. Those three classes were (1) households experiencing sudden and significant losses of income, (2) households gaining new members and (3) households with no income. Under the 1980 Amendments, the Secretary also had authority to exempt or modify the retrospective approach for "other classes of households" where retrospective procedure would "be impractical to administer or would cause serious hardships * * *." Under the 1981 Reconciliation Act version those three specific classes of households are not mentioned. Instead the Department is required to provide for increases in allotments for newly applying households which would otherwise suffer "serious hardships."

Both the 1980 Amendments and the Reconciliation Act contained essentially the same provisions regarding the computation of income for households receiving benefits under both the Food Stamp Act and Title IV–A of the Social Security Act. However, the Reconciliation Act added an explicit waiver provision that authorizes the Department to waive provisions of the retrospective accounting section of the Reconciliation Act "to the extent necessary" to permit States to calculate food stamp income "on the same basis" as income is calculated under Title IV–A of the Social Security Act.

The Department interprets that explicit statutory waiver as conferring discretion on the Department to make such waivers on a State by State basis after an examination of the appropriate circumstances. While public comment on this waiver authority will be examined, such a statutory provision is effective without rules. Additionally, the Department believes that public comment would be unnecessary to the Department's ability to carry out its provisions.

Another similarity is that under the Food Stamp Act, as amended by both the Reconciliation Act and the 1980 Amendments, income earned on a self-employment or similar basis which provides a household's annual income (even though earned in less than a year) is to be averaged over a 12 month period. For example, under both the 1980 and 1981 versions self-employed farmers would have their farm income averaged over a 12 month period. Under both versions, the same would be true of scholarship, loan or grant monies received by students except that such income would be averaged over the student's school year or semester.

The changes made by the Reconciliation Act to the periodic reporting provisions of the 1980 Amendments are precise. Those changes require that certain classes of households file periodic reports and also exempts certain specified classes of households from the reporting requirements. The Reconciliation Act also mandates that a household shall not receive benefits for periods of time for which they were required to, but did not, submit a periodic report.

**Background**

Two key issues in the delivery of assistance benefits to poor persons are the determination of their needs and the handling of changes in the household's circumstances. There have been two general approaches for each issue.

In determining need, household circumstances have been considered on a prospective or retrospective basis. Prospective budgeting or accounting (the terms are interchangeable) means looking ahead to the time period, for example May, when benefits will be issued, and trying to determine how much assistance the client will need in May. Under this system, the client's projected financial capacity in May plus the assistance issued in May should respond to the client's projected needs in May. However, because both the household and the State agency are anticipating circumstances, a household's needs and the assistance it receives may not match. When this happens, it is normally cost-inefficient to later determine the difference and to make up an underissuance or attempt to recover a surplus.

Retrospective budgeting means looking back in time to determine what a client's actual financial capacity was in the past (March, for example), and issuing benefits in May which, added to that capacity, should equal the client's needs. Under the retrospective approach, the client's own financial capacity in May, plus the assistance issued for May (but based on March) may equal the client's needs in May. As with prospective accounting the total may exceed the client's needs in May or fall short of them. Over the long run, however, a household's needs should be met more exactly under the retrospective approach than under the prospective budgeting approach.

Whichever approach is used there is the question of how changing circumstances are to be handled. One response is to require the reporting of changes by the household. For example, when income rises or falls the client would report it. This approach is usually used with prospective budgeting since the provider of the assistance could look forward to determine the effect of the reported change on future benefits.

The other approach, which is called periodic reporting, depends upon reports which a client submits on a regular basis. Under periodic reporting, the State agency may require a client to report even if nothing has changed. Each of these approaches has its own advantages and disadvantages.

In the 1980 Amendments as later amended by the Omnibus Budget Reconciliation Act of 1981, Congress adopted a retrospective budgeting and periodic reporting system for most food stamp households. These rules will require such a system for the first time for food stamp recipients.

**Implementation**

The Reconciliation Act of 1981 requires all State agencies to implement the MRRB system no later than October 1, 1983. Between now and October 1, 1983, State agencies may continue the current prospective system. In the intervening months, State agencies may phase-in this rule. This phased implementation may be done in any reasonable manner based on geographical, project area, or political boundary consideration, or on the basis of types of households—such as AFDC or General Assistance cases. This implementation rule is based on State agency comments requesting added flexibility to enable States to phase-in the MRRB approach more smoothly and efficiently.

The proposal required each State to solicit public comment prior to implementing a MRRB system. These interim final rules have dropped that requirement. In its comment letter Michigan pointed out that, in light of the regulatory comment period and the FNS

hearing on these rules, the requirements in the proposal for States to seek public input prior to implementing MRRB would not be worth the expense involved. Most public interest group comments, such as "Food Emergency Action Development" of Connecticut, supported additional public input at the State level. On the other hand a commenter noted that additional comment on "operational procedures * * * invites endless debate over details on system design which must be treated as an integrated whole rather than dealt with in isolation." The Department agrees and has eliminated the proposed requirement that States seek public input prior to implementation.

In the proposed rule the Department required State agencies to conduct a successful test before implementating MRRB. Some State agencies wanted the test requirement automatically deleted if the State agency were already running a MRRB system in its AFDC program. Interest groups generally supported the idea of a test, stating that operation of an AFDC–MRRB system should not excuse a food stamp trial run. Interest groups also stated that the test should be limited to a small geographical area so that only a few recipients would be hurt if the MRRB system proved to be inadequate.

Under these interim rules FNS approval of the State agency's MRRB system must be obtained prior to implementation. The State agency must present FNS with evidence that it can effectively operate a MRRB system that participating households can understand. This evidence must be derived from one of two sources. Unless FNS permits otherwise, the State agency must conduct a limited test of its system and submit the results to FNS. In the alternative, if a State agency operates a MRRB system in its AFDC Program, FNS may waive the test and evaluate the AFDC–MRRB system in place of the test.

The Department believes that some testing may be necesary in view of the large number of procedures which a State agency will have to implement. However, the circumstances of each State agency's implementation will be different. Some may implement MRRB statewide, others may phase it in only for certain project areas. For these reasons the final rules are not overly specific. In the event that FNS determines that a State agency's AFDC–MRRB is an adequate substitute for a test, FNS will waive the requirement for a separate test as unnecessary.

In selecting options which the Department is offering through this rule, State agencies may implement a single option across the entire State, or may choose different options for separate project areas.

**Definitions**

Because the MRRB system represents a departure from the prospective budgeting methodology, a new set of definitions specifically tailored to that MRRB system has been developed. Comments regarding the proposed definitions are analysed under the appropriate heading.

*Adequate Notice of a Reduction or Termination of Benefits:* Of all the proposed definitions, this one received the most comments. In the proposed MRRB system each State had to provide the household with written notice when the State intended to lower or to terminate the household's food stamp allotment based on the household's monthly report. Further, that notice had to advise the household of the basis for the State's action and of the household's appeal rights. The notice also had to arrive no later than the date a household would expect to receive its allotment or ATP card. Two legal assistance groups and three interest groups criticized this provision and stated that notice should always arrive before the expected allotment, rather than in place of it or accompanying it. Legal assistance groups cited *Goldberg* v. *Kelly*, 397 U.S. 254 (1970) for that proposition.

When a household submits a monthly report, these interim rules require the State agency to process the report and then notify the household of the report's effect. As proposed, this notice must be sent to the household so that it will be received by the household by the same time it receives its allotment or in place of the allotment if the State agency has terminated the household. While this notice may not inform the household in advance of any change, it is adequate in that it details the change, its cause, explains the hearing appeal process, and provides an opportunity for the continuation of benefits.

The Department believes that due process does not require advance notice under this MRRB system. (Moreover, as explained later the mechanics of operating a reponsive MRRB system make advance notice difficult if not, at times, impossible to deliver.) These regulations require, where a household challenges its monthly benefit level within 10 days after the State mails benefit notification, that the household receive a second allotment, by the end of five business days, equal to the amount of the reduction in benefits. The Department believes that this approach is in excess of minimum due process requirements since, under the statute, retrospective accounting benefits are provided solely on a *variable basis* as determined by the household's monthly report. Households (contrary to the prospective accounting system where households normally expect the same benefit level each month during the certification period) will be clearly advised in the MRRB system that benefits will vary or be terminated based on their monthly reports. The statute thus creates an entitlement system based on "automatic" mathematical monthly adjustments in benefits determined by *household input.* Moreover, each household will be advised that benefit levels are only guaranteed for one month. In effect, each participant's property interest in a certain level of benefit is recomputed on a monthly basis and is mathematically varied according to household input.

We believe that the holding of *Goldberg* v. *Kelly* is not applicable to this situation. *Goldberg* struck down procedures allowing termination of a household's AFDC assistance based on a caseworker's judgment, without prior notice to the household, without provision for continuation of benefits, and where the recipient could be "condemned to suffer grievous loss." (397 U.S., at 263.) Under these regulations, households have an opportunity to request supplemental payments which will provide them with aid pending the resolution of the dispute. Also, the adjustments to the benefits levels are based on data provided by *the affected household.*

The household will be advised by the reporting form of the criminal consequences for intentional misrepresentation regarding that household data. The household data is then inserted into a mathematical formula for computing the household's entitlement for the next month.

In a sense, each month in a MRRB system is similar to the beginning of a certification period under the current food stamp regulations. Under the current prospective accounting system there would be no "continuation of benefits" for initial applicants, pending resolution of a fair hearing, since there is not continuing prior entitlement to a certain benefit level. Challenges, for example, to an alleged incorrect initial benefit computation would simply be resolved, under the current system, at a subsequent fair hearing without any prior notice of "adverse action" and without any "increase" in benefits pending the fair hearing resolution. (For additional analysis of related due process issues see *Mathews* v. *Eldridge*, 424 U.S. 319 (1975); *Velazco* v. *Minter*,

481 F. 2nd 573 (1973); *Harrell* v. *Harder*, 369 F. Supp. 810 (1974); and 127 *Cong. Rec.* S5911, daily ed., June 9, 1981.)

On this same point it should be mentioned that section 6(c)(2)(A) of the Food Stamp Act requires State agencies to issue an allotment within thirty days of the end of the budget month unless the Department finds that a longer period of time is necessary. This represents a very tight time limit for the millions of households that must be processed monthly. Second, section 6(c)(2)(D) of the Act requires the State agency to give a household extra time to file a complete report if it has failed to do so by the reporting deadline. Third, section 6(c)(4) of the Food Stamp Act prohibits a State agency from issuing an allotment until a household submits its monthly report.

The short time period for taking action on a report, the requirement that the State agency extend the filing period and the prohibition against issuing an allotment without a report combine to make advance notice impractical for both recipients and State agencies alike. State agencies cannot efficiently issue the increased or unchanged allotments on one schedule and the reduced allotments on a later schedule. An alternative might be to delay all issuances to the forty-fifth day after the end of the budget month. However, the House of Representatives Committee on Agriculture generally discouraged such an approach unless clearly necessary (House Report No. 96–788, 96th Congress, 2d Session, page 91). As an additional point the 96th and 97th Congresses viewed the MRRB system as a vehicle for jointly administering the AFDC and Food Stamp Programs to the greatest extent possible. The AFDC Program's regulations allow adequate, but not prior, notice (see 45 CFR 233.37(b), 46 FR 46767; September 21, 1981). The AFDC notice must be received no later than the date the household would receive its AFDC grant.

In summary of this important issue, it should be emphasized that the whole nature of the food stamp program has been changed by the MRRB approach. Instead of the typical food stamp household expecting to receive a fixed amount of monthly benefits for several months (during the certification period) recipients are now only entitled to benefit levels *as mathematically adjusted monthly* (if necessary) based on the *participant's* monthly reporting of *factual data.* The report form that the participant must file warns the household that the information provided may result in the reduction or termination of benefits. Additionally, an opportunity for the continuation of aid pending resolution of the dispute is allowed.

*Beginning Month:* A new definition is added by these rules for the purpose of handling special hardship cases. "Beginning month" will mean the month a household applies for stamps, and, in some cases (as explained later), will also mean the month after that month. However, a beginning month can never be any month which immediately follows a month in which a household is certified. (The Department uses a similar phrase, "initial month," for purposes of prorating a household's allotment. A particular month may be a beginning month for MRRB purposes and an initial month for proration purposes.)

*Budget Month:* No significant comments were received regarding the budget month concept which, as mentioned in the proposal, is an integral part of the MRRB program. As in the proposal, the budget month is the month about which a household reports. The household's circumstances from this month determine the allotment for a later month. When a household submits a monthly report to the State agency, it is reporting about the budget month. The State agency then uses this information from the budget month to calculate the household's food stamp allotment for a later month, the issuance month. The budget month may be a calendar month or a fiscal month.

*Issuance Month:* In the proposed as well as this final definition the issuance month is the month for which a State agency issues an allotment. In retrospective budgeting, this month's allotment is based upon a household's income, deductions, and other circumstances from a previous month, the budget month. (In the AFDC Program, the issuance month is called the payment month.) It should be noted that a State agency may issue an allotment for the issuance month after the end of the month. This will occur when either the State agency or the household is responsible for a delay. Therefore, the issuance month is not the month *in* which a State agency issues an allotment, but the month *for* which it issues an allotment to a household. Vermont suggested that this clarification be made in the final definition to avoid confusion.

*Prospective Budgeting:* Also called prospective accounting, this is the budgeting procedure which the food stamp program has used in recent years. Prospective budgeting means that an eligibility worker looks forward in time to anticipate what a household's circumstances will be, including its size and composition, its income and deductions, or its other circumstances. Although this interim rule subjects most households to retrospective budgeting, migrant farmworker households and household facing serious hardship will continue to have their circumstances budgeted prospectively. As an example, such a household's allotment for March would depend upon its expected circumstances in March.

An additional difference between this rule and the proposal is that this rule permits State agencies to determine *eligibility* prospectively. That is, eligibility for a household in March could be based upon March income, even though its allotment would depend upon January income. By using a prospective determination of eligibility, a State agency can terminate a household's participation rapidly when the household's economic circumstances improve to such an extent that it no longer needs food stamp assistance.

*Retrospective Budgeting:* As required by amendments to the Food Stamp Act of 1977, this rule permits State agencies to budget most household circumstances retrospectively. This means that an eligibility worker looks back in time to see what a household's actual circumstances were, and then uses that information to calculate a future allotment. For example, an eligibility worker would use a household's income and deductions from the budget month of March to calculate the household's allotment for the issuance month of April or May.

A difference between this rule and the proposal is that most households will now begin retrospective budgeting in the month of application. When a household applies in March, its allotment will depend upon its January circumstances (in a "two-month system" as described below). Under the proposed rule, retrospective budgeting would not have applied in a household's "beginning month" of participation. Thus, under the proposal a household could have been eligible based upon its circumstances in the month of application (even if not eligible based on a prior month's circumstances) and therefore would not have had to wait one or two months to be certified. In this interim rule, the effects of delayed participation for households determined retrospectively ineligible may be alleviated through the availability of "serious hardship" procedures described later.

*Choice of Options:* Sections 5(f) and 6(c) of the Food Stamp Act give the Department two important choices in designing a MRRB system. The choice

between retrospective and prospective determinations of eligibility is one. The choice between a one-month system and a two-month system is another. Because the different State agencies have a variety of MRRB systems in their AFDC programs, the Department is passing these choices on to the State agencies. In this way the State agencies can make their food stamp and AFDC programs consistent.

The choice of less consistent options could increase the administrative costs of both programs. Therefore, to keep administrative costs down, each State agency must choose the more consistent option. For example, if a State agency determines AFDC eligibility prospectively, it must determine food stamp eligibility prospectivley. If a State agency operates a one-month AFDC system it must operate a one-month food stamp system.

It is possible that State agencies will have good reasons for wanting to choose options which are less consistent with AFDC. The State agency could choose the less consistent option only if it requested a waiver from FNS. FNS will approve the waiver if it is needed to improve the Food Stamp Program's administration or to make the program more cost effective.

**Included and Excluded Households**

Under authority of the 1980 Amendments, the proposal stated that four categories of households would be excluded from the MRRB system in addition to migrant farmworkers. These categories were (1) strikers not certified for food stamps prior to the strike, (2) households containing elderly and disabled members without earned income, (3) households only temporarily eligible for food stamps, and (4) households requiring special assistance (such as retarded persons) in applying for food stamps. The Reconciliation Act, however, deleted the list of groups for which the Department could make MRRB "exceptions" and instead required that migrant farmworkers have their benefits calculated on a prospective basis. No other classes of households were exempted although the Reconciliation Act provided that benefit levels could be adjusted for newly applying households where "serious hardship" would otherwise result.

The Reconciliation Act also exempts households from monthly reporting but not from retrospective budgeting if they have no earned income and if all household members are sixty years of age or over or receive supplemental security income benefits or disability or blindness payments under specified titles of the Social Security Act. These regulations, for administrative convenience, also provide that the State agency may exempt from monthly reporting "households whose *adult* members are all without earned income and are at least sixty years old or receive SSI or disability and blindness payments" under specified titles of the Social Security Act. However, the State agency may not exempt these households if they file monthly reports for the AFDC program.

The December 5, 1980, proposal elicited numerous comments on the types or classes of households which should receive special treatment under the MRRB system. Those comments were carefully reviewed, but reviewed in the context of the precise requirements of the Reconciliation Act.

Many of the State commentors wanted the Department to provide them with the authority to determine the special circumstances which would allow adjustments to the normal MRRB system. Their view was that the individual caseworkers or local agencies were in the best position to determine the need for special adjustments to the normal MRRB method of computing benefits or determining eligibility. These rules provide some State flexibility regarding "serious hardship" cases as discussed later in this preamble.

**Retrospective Budgeting**

The Food Stamp Act, as amended by the Reconciliation Act, requires that State agencies calculate retrospectively the allotments of all households except for "migrant farmworker households." Consistent with the proposed rule and with the House Report on the Reconciliation Act (H. Rept. 97–106), the Department has excluded only those migrant households which are in the job stream. When such a household returns to its home, it ceases to migrate. At that time it becomes subject to retrospective budgeting and to monthly reporting. When the household again migrates, it becomes a migrant farmworker household and must be excluded from MRRB. The House Report focuses on the "mobility" of migrant farmworkers and the complications arising from attempting to verify income and circumstances from a past period "when they are not residing in the project area." (H. Rep. 97–106, at p. 33). The comments from the Nebraska Association of Farmworkers and the Delmarva Rural Ministries also support the distinction between migrants in the migrant stream and other migrants.

Consistent with the Act, the Department has included three other classes of households (households that derive their annual income in a period of time shorter than one year by contract or by self-employment and households receiving nonexcluded education assistance) in all facets of MRRB except with regard to the specific kinds of income which the Act mentions. Therefore, these households will have their contract income, self-employment income, or nonexcluded scholarship income proprated over the appropriate number of months. Their other circumstances, like deductions and *other* income, will be budgeted retrospectively. States urged the Department to make the new MRRB rule as universal as possible to avoid confusion and to make computer processing easier.

**Monthly Reporting**

As mentioned earlier, the Reconciliation Act requires State agencies which use a MRRB system to require certain categories of households to submit periodic reports of their circumstances. The Act specifies the categories which must be reported periodically. They are: all households with earned income, all households with potential earners (including individuals receiving unemployment compensation benefits), all households required to register for work in the Food Stamp Program, and all households which are required to report periodically for the AFDC Program. The 1980 amendments allowed the Department the authority to decide which categories of households had to file periodic reports. While a number of comments were received regarding the types of households that should be required to file periodic reports, these final rules carefully follow the precise requirements of the Reconciliation Act. (Nonetheless, useful information was derived even from comments superceded by the Reconciliation Act in terms of the problems which certain types of households might encounter in filing monthly reports.)

The legislative history suggests that the households excluded by the Reconciliation Act, migrants and households whose only adult members are elderly or disabled (as defined earlier) without earned income, would be burdened unfairly by submitting monthly reports. For the purposes of this rule, the Department is requiring all households to submit monthly reports except for those households which Congress has specifically excluded. Thus, each non-exempt household will submit a report for one month which will determine that household's allotment one or two months later. In the event a State agency wishes to

exclude additional households from monthly reporting it may request a waiver from FNS. However, under any State agency's system, those households which Congress has included in monthly reporting cannot be excluded.

**Special Assistance**

Section (6)(c)(2)(B) of the Food Stamp Act requires that State agencies make available special assistance to households which need it. Specifically, the Act requires assistance for any household whose adult members are all mentally or physically handicapped or are so lacking in reading and writing skills that they cannot complete the required reporting form. These rules indicate the State agencies are to determine who fits into those categories. The special assistance to be provided by the States could include a special telephone number for households to call to report information, home visits by eligibility workers, or special arrangements for reporting in person at the food stamp office.

**Information on System Operation**

Because MRRB can be a complicated system for households which are not familiar with it, State agencies must explain the system to the households. The Department is requiring the State agencies to give each household a copy of the monthly report form, along with instructions on how to complete and submit it. Included in these instructions must be an explanation of the State agency's verification requirements. Finally, the State agency must provide the household with a local or toll free telephone number. By calling this number clients will be able to ask questions about MRRB and obtain help in completing and filing their reports. Many public assistance commenters requested that such telephone assistance be made available.

**One Month System**

Under these interim rules a State agency may design either of two MRRB systems. In the "one-month system," the issuance month (May, for example) immediately follows the budget month (April). The one-month system thus had one "beginning month" of participation (May) during which increased allotments could be issued for households in "serious need". The term "beginning month" was developed to identify those months in which new applications in "serious need" could receive benefits based on *prospective* factors. This approach is discussed later in this preamble.

**Two-Month System**

The other system is the "two-month system." In this system, the budget month (March, for example) determines the allotment for an issuance month which is two months later (May). The intervening month allows the State agency more time to process the report. In this two-month system there are two "beginning months" of participation.

California strongly supported the concept that States have the option of adopting either a one-month or a two-month retrospective system to achieve greater consistency with AFDC income rules. California stated that the proposal "seem(ed) to imply * * * that a one or two-month system could be used." These final rules make clear that States have this option. The Department gives State agencies this choice based upon section 6(c)(2) of the Food Stamp Act. This provision of the Act permits the Department to determine if a two-month system is necessary. It is evident to the Department that such a system may be necessary. Therefore, State agencies have this option.

In order to keep a household from leaving the program (and MRRB) and reentering under prospective eligibility whenever it is in the household's advantage, the Department is restricting the definition of the "beginning month." A month cannot be a "beginning month" (for which supplemented allotments are allowed for households in "serious need") if the household was certified in the immediately preceding month. This is true even if the State agency has suspended or terminated the household's participation or if the household had been certified in the preceding month but did not participate.

**Determining Eligibility and Allotments in the "Beginning Months"**

In developing the MRRB system the Department is using retrospective budgeting to determine benefit levels for the month of application for most households. This means that a household which applies in March would, except for cases in which special procedures are applied, have its March allotment based upon its January circumstances.

However, the Reconciliation Act provides for the supplementation of allotment levels for "newly applying" households where "serious hardship" would otherwise result. The Department intends to supplement those allotments by requiring State agencies to use prospective budgeting in the "beginning months" for those households.

Under these rules, households eligible to receive enhanced allotment levels include those households which are entitled to expedited service under 7 CFR 273.2(1) (households with zero net income or households which are destitute), households gaining a new member, and other types of households as determined by the State agency. For these households the State agency would determine eligibility based upon prospective budgeting for the month of application. For example, if a household applies in March and has no net income in March, or is destitute in March, it is entitled to prospective budgeting in March (and in April if there are two beginning months). Note that these special rules only apply to "beginning months."

Included in the serious hardship situation, as mentioned above, are households gaining a new member in the month of application. For example, if a household gained a new member and applied in April it would not be fair to base the allotments for April and May on the smaller household size in February and March. This household size rule is also justified to achieve greater consistency with the AFDC Program which has a similar procedure.

It should be mentioned that comments were received on how the Department should handle cases where "serious hardship" would result from following a purely retrospective budgeting approach. As the comments made clear, households in this hardship category could often include those which had income in the prior month but which lost that source of income for the issuance month. An appropriate response to such cases is one which focuses on "current" income, that is income in the issuance month. These interim rules adopt such an approach.

For these serious hardship cases, the Department considered whether to develop procedures for a second issuance of benefits or to establish procedures for issuing a modified single allotment. Based on the administrative complications (computer processing and added workload) regarding the second allotment approach, the Department decided that it would be efficient to have States deliver a single, but modified, allotment level.

Based on the comments, these interim rules allow State agencies to expand the definition of "serious hardship" to include other categories of households as well as the two specified categories. In this way States will be given the opportunity to tailor these provisions to the needs of their caseloads. However, the Department is specifying certain categories of households which cannot receive this special prospective

budgeting. These are households which have caused their own decreases in income. The Department does not believe that these persons should be rewarded by receiving enhanced benefit levels for themselves and their families. For example, a household containing a striker would not be defined as experiencing "serious hardship" under these rules, nor would a household containing a member who had quit work or who had voluntarily reduced the number of hours worked.

Finally, these rules provide that States may not include as "serious hardship" cases those households whose assistance grants, Supplemental Security Income (SSI) payments or similar payments had been reduced to recover overpayments. Many of these households may have received overpayments because of household fraud. It is conceded that some of these households may have unknowingly received higher SSI or other payments than they should have received. Nonetheless, the Department does not feel that households which had previously received a series of overpayments would normally present a serious hardship situation. Also, it was impossible to develop an efficient rule capable of distinguishing between "innocent" households suffering recoupment of prior overpayments and households which had contributed to the situation requiring recoupments.

**The First Month of Retrospective Budgeting for "Serious Hardship" Cases**

These rules provide that the State agency shall not take into account the household's "noncontinuing income" (income received in a prior month from a source which will not provide additional income to the household in later months) in determining eligibility or in calculating the allotment for the *first month* in which retrospective budgeting is used. A household may lose all its income in March, apply for stamps in March, and receive benefits on a *prospective* basis for March and April. Its May benefits would then be *retrospectively* based on its circumstances in March. If noncontinuing income were included in the calculations, the special treatment accorded the household in the initial month would be negated when the noncontinuing income is subsequently counted. Therefore, noncontinuing income from the month of application will be disregarded in calculating food stamp allotments for these households.

In the AFDC program, the State agency disregards noncontinuing income for the first two months of retrospective budgeting (see 45 CFR 233.35(b); 47 FR 5679, February 5, 1982.) The food stamp provision is based upon the Department's definition of serious hardship in the beginning months. If a State agency were to use the AFDC procedure in the beginning months (prospective budgeting for all households), the State agency would also use the AFDC procedure for noncontinuing income.

**Determining Eligibility**

Based on the comments, this final rule gives a State agency two options for determining eligibility. In the first option, the State agency would prospectively determine *eligibility*, even though *issuance* would be determined retrospectively. For example, if March were the budget month and May were the issuance month, and a household reported a substantial increase in stable income in mid April, the State agency would terminate the household as ineligible as of the last day of April. This would be true no matter what the household's circumstances were in March, the budget month.

In the second option, the State agency would retrospectively determine eligibility. Eligibility in the issuance month (May in the example) would depend upon all eligibility factors as they existed in the budget month (March).

There are advantages and disadvantages to each option. In retrospective eligibility there is a lag time between an event which makes a household ineligible and the State agency's termination of the household. In prospective eligibility the lag time is minimized. However, a State agency which determines eligibility prospectively will have to obtain more information from the household and perform two calculations—one for eligibility based on the issuance month and one for the allotment based on the budget month.

Another issue raised by the comments is whether a State agency could compute benefits using information that is in part anticipated and in part retrospectively determined. The proposed rule required State agencies to compute benefits using information from the budget month, with the exception of certain averaged amounts. Many State agencies suggested that they be allowed to mix prospective and retrospective accounting. For example, if January were the budget month and March were the issuance month, they might compute March's allotment using January's earnings but also using medical expenses which the household anticipates for March.

The Department does not believe that the Act permits mixed accounting techniques. Moreover, mixing prospective and retrospective accounting requires anticipation of frequently unverifiable future events. MRRB is viewed as an alternative to prospective accounting and the problems which prospective accounting entail. The rule does not allow for mixing accounting methods.

**Certification Period**

The Reconciliation Act gave the Department the authority to waive the current limit of twelve months for certification periods where that would "improve the administration of the program." The Department is not prepared to issue waivers at this time in context of monthly reporting. The Department is cooperating with the Department of Health and Human Services and the Illinois Department of Public Aid in conducting a demonstration project. Among other aspects of MRRB, this project will test the effect of an indefinite certification period on error rates. When the Departments complete their work on the demonstration project, and based on the comments received regarding this rule, the issue of the 12 month limit on certification periods will be reexamined.

The Food Stamp Act (section 3(c)) requires State agencies to certify monthly reporting households for at least six months. The Congress set this minimum because monthly reporting is a satisfactory substitute for brief certification periods (House Report No. 96–788, 96th Cong., 2d Sess., p. 94). Short certification periods monitor households with fluctuating circumstances or households whose circumstances are expected to change. A monthly reporting system serves the same function. Therefore, this rule sets a minimum certification period of six months for these monthly reporting households.

**Waivers**

The Food and Nutrition Service published final regulations on January 21, 1981, concerning waivers of Food Stamp Program regulations (see 7 CFR 272.3(c)). The regulations state that FNS shall not approve any request for a waiver when the waiver would be inconsistent with the provisions of the Act.

When Congress enacted the Omnibus Budget Reconciliation Act of 1981, it recognized that an efficient Food Stamp MRRB system depended on consistency with an efficient AFDC–MRRB system. Congress also recognized that some of the statutory provisions concerning

retrospective budgeting for the Food Stamp Program might conflict with AFDC procedures. Therefore, Congress included in section 5(f) of the Food Stamp Act a precise expansion of the Department's waiver authority. The Department may, if necessary for a State agency to calculate income in the Food Stamp Program as it does in its AFDC Program, waive any of the section 5(f) provisions. Specifically, section 5(f) describes prospective and retrospective budgeting, the prorating of income, special provisions in the beginning months of participation, and the exclusion of migrant farmworker households from MRRB. In particular the Department will waive the requirement for retrospective budgeting when a household applies. The Act specifically grants this waiver authority to the Secretary who is to exercise discretion based "upon the request of a State agency."

The Department is amending 7 CFR 272.3(c) to include the waiver provided in section 107(a) of the Reconciliation Act as discussed above. The Department is not requiring public comment on each waiver. This approach will expedite the waiver process and will allow States to utilize public comment as they determine appropriate.

**Calculation of Allotments**

*Household Composition*

The household composition for which the State agency calculates an allotment must match the household which is determined eligible. If a five person household is eligible, the State agency must calculate an allotment for that same five person household. Therefore, under retrospective eligibility and as proposed in the December 5 rulemaking, household composition is determined as of the last day of the budget month.

Under prospective eligibility, the State agency will use the household's composition as it will be during the issuance month. The Department is not specifying a particular date during the issuance month. The State agency can look at the entire month and take into account whatever changes are likely to occur in the issuance month.

In a two month system, if the household gains a member in the month between the budget and issuance months, and the household reports this change, the State agency will determine eligibility using the household composition as of the issuance month. This will occur even if the State agency would usually determine eligibility retrospectively. This procedure is similar to one in the AFDC Program (see 45 CFR 233.35(a)). Its purpose is to allow the new household member to receive food stamps. The Food Stamp Program's other regulations on household composition (7 CFR 273.1) would make it impossible for many such individuals to separately receive food stamps, even for one month. So that these individuals are not excluded from the Program, the Department has adopted this procedure.

*Income and Deductions*

The State agency shall use the household's income and deductions from the budget month, or as they are prorated for the budget month, in this MRRB system. Under this rule, as under the prior rules and as specified in the Act, there are three forms of income which the State agency must prorate on a monthly basis. This is done to avoid alternating a household between periods of ineligibility and eligibility.

The first kind of income that must be prorated is self-employment income which is received less frequently than monthly. The State agency must average such income over a twelve month period and consider each monthly amount as one-twelfth of the annual income. The second kind of income that must be prorated is income received by contract in less than one year. The State agency will also "annualize" this income by taking the yearly total and dividing by 12. The third kind of income to be prorated is income for education, such as nonexcluded scholarships, deferred educational loans, and other education grants. The State agency will prorate this income over the period it is intended to cover, such as a semester. As mentioned earlier, these rules are required by statute.

*Monthly Reporting*

If a household is subject to monthly reporting, the State agency shall require the household to report its circumstances each month. The Department has discretion over the frequency of reporting. We have chosen monthly reporting for a number of reasons. First, as mentioned in the comments, monthly reporting matches the Program's system of monthly issuance. Second, monthly reporting is simple for households; they need not remember a complicated schedule. Third, the House Report on the Food Stamp Act Amendments of 1980 (House Report No. 96-788, 96th Congress, 2d Session, pages 87 to 94), repeatedly refers to monthly reporting as the basic reporting system for retrospective budgeting. Fourth, the AFDC Program uses a monthly reporting system (see, 45 CFR 233.36, 46 FR 46767, September 21, 1981).

These rules require that the State agency provide assistance to households in the completion of monthly report forms. As proposed, this must be done in two ways. First, the State agency must have available an individual or office to answer promptly questions about monthly reporting. Second, the State agency must provide a local or toll free telephone number for households to call for assistance. Many commenters felt that these requirements would be essential to the smooth operation of monthly reporting system.

As proposed, these final rules require that the monthly report form clearly indicate the information that the household is expected to report. The report must further comply with the Program's bilingual requirements (see 7 CFR 272.4(c)), specify the reporting deadline, the consequences for not filing on time, and the possibility that the household's issuance could be delayed if the household does not timely submit the report. The form must also remind the household of the Program's verification standards.

The report form must contain a statement for a responsible household member to sign showing that the household understands that the State agency may change its allotment because of the changes which the household reports. (Iowa, Texas and Nevada emphasized that it was inefficient to permit only the head of the household to sign the form.) The monthly report form must also indicate the telephone number which a household may call for assistance and the unit or agency which will provide that assistance.

The report form must contain a statement which describes the Food Stamp Act's civil and criminal penalties for fraud. This statement is required by section 6(c)(3) of the Act. The description must be prominent and appear in bold face lettering. A similar provision has appeared on the change reporting form since 1979, as required by 7 CFR 273.12(b)(1)(ii).

Finally, in accordance with the Privacy Act of 1974 (Public Law 93-579, Section 3(e)), the State agency must explain the requirement that the household must provide its members' Social Security number's (SSN's). The explanation must first contain the authority to obtain the information. That authority is Public Law 96-58 (7 U.S.C. 2025 F), the 1979 Amendments to the Food Stamp Act of 1977. The providing of SSN's is mandatory, in accordance with 7 CFR 273.6. Second, the explanation must contain the purpose of requiring SSN's. That purpose is to

ensure the accuracy of benefits for eligible households. Third, the explanation must contain the routine uses of SSN's. The routine use is computer matching to prevent duplicate participation, to check the identity of household members and to make mass changes. If a household member refuses to provide a SSN, that member is ineligible to participate in the Food Stamp Program.

*Reported Information*

The proposed rule required the following information on monthly reports: name, address, household composition, nonexcluded income (unless averaged), shelter costs (unless fixed costs are retained by the state agency), medical costs exceeding $35, dependent care costs, liquid resources exceeding $1,500, and the acquisition of an automobile. There were many comments on this provision.

Some State agencies wanted households to report everything in a particular category (all income, all medical expenses). In this way households would not have to decide what should be included and what should be excluded. One State agency wanted to delete the requirement that stable elements of all types be reported. Legal assistance groups and interest groups wanted a form designed to let households check "No Change" rather than completing the entire form. This would ease completion of the form, particularly for households with problems of illiteracy. One interest group wanted to require State agencies to retain fixed shelter costs. (By comparison, AFDC does not specify what information State agencies must seek.)

Additional options in this regard include the *monthly* reporting of some factors and the *periodic* reporting of other factors, the reporting of just certain factors (income and composition) or the reporting of events (changes reported within ten days). The House Report on the 1980 amendments (*H. Report.* 96–788, p 89) mentioned that the Secretary should specify the form's contents, but suggested that the form not request irrelevant information.

The least complicated requirement for most households is the reporting of all information about income and deductions. State agencies would then use that data as the specific regulations require. That reduces the likelihood that households will improperly determine what is relevant information. The problem with this approach is that households would then be gathering documentation to verify some irrelevant information. These same arguments, in favor and against, apply to the non-reporting of stable information, averaged information and fixed shelter costs. Reporting only changed information would mean easier completion of the form and easier processing. There is, however, significant value in having a recipient deliberately complete an entry for each factor of eligibility. It avoids a recipient's automatically checking "No Change" no matter what has taken place. A household in a hurry, or one having problems completing part of the report, might otherwise be tempted to report "No Change."

The interim rule on monthly reports requires that State agencies ask for certain information regarding the budget month. The State agency will require each household to report budget month income, deductions, household composition, and other household circumstances which affect food stamp allotments. The State agency will also ask about changes which can affect a household's eligibility. This information may be about the budget month or about later months. The State agency would use future information to determine eligiblity prospectively.

To increase program efficiency, these interim rules provide that the State agency can combine the food stamp monthly report form with the AFDC form. However, the State agency must indicate that non-AFDC food stamp households do not have to answer purely AFDC questions. Of course, the State agency could not reduce or terminate any household's food stamp eligibility because it did not answer a question related only to AFDC.

*Household Composition Changes*

A question arose regarding what information should be reported when a household's composition changes. The proposed rule would have required a household to report its composition as of the last day of the budget month. The interim rule also contains this provision. If a household member leaves the household before the end of the budget month, that member's income and deductions are not reportable and will not affect the allotment for the appropriate issuance month. Conversely, if a new member joins a household during the budget month, even at the end, that member's income and deductions are reportable and will be reflected in the appropriate issuance month's allotment. This policy increases the likelihood that the "household" about which the report is filed is also the "household" to which benefits are issued. A consistent, uniform policy is needed to insure that no individual who moves from household to household has income counted twice or not at all.

*Submitting the Monthly Report Form*

The State agency may set its own deadline for the household to submit its monthly report. However, this date must provide the household with a reasonable period to report after the end of the budget month. State agencies are encouraged to set this deadline as late as possible to avoid the need for sending reminder notices to households and to avoid disruption of the issuance schedule.

The proposed rule would have required State agencies to provide households with postage-paid envelopes for returning monthly reports. This requirement reflected the concerns of the House Committee on Agriculture (H.R. 96–788, 96th Cong., 2nd Sess., page 91). The Committee felt that these envelopes would insure the prompt returning of the reorts. At that time (1980) the AFDC Program had a similar requirement.

Some State agencies commented that this requirement would be a burden to them. Other commenters supported the requirement. The Department of Health and Human Services removed this requirement from AFDC on September 21, 1981 (see 46 FR 46759).

In the interest of consistency with AFDC, this Department is not requiring State agencies to provide postage-paid envelopes. However, should the State agency choose to provide them, the Department will reimburse the State agency for its administrative costs according to the usual formulae.

*State Agency Action on Reports*

The MRRB regulations on State agency action on household reports deal with four topics: (1) the normal processing or a report when a household submits it by the initial filing date, (2) the verification which the household must provide, (3) the nature of the notice which the State agency must send each household, and (4) the State agency's procedures for processing a report which the household does not submit on time.

*Processing*

When the State agency receives a monthly report, it must review it for accuracy and completeness. Under these rules, a report is incomplete if the household's head, authorized representative, or responsible member has not signed it. Second, it is incomplete if the household has not verified income. Third, a form is incomplete if the household has omitted

information which is necessary either to determine eligibility or to calculate an allotment.

The State agency must also determine if any verification is missing. In addition, the State agency must determine if it needs any additional information because the household has reported a change. For example, a household might report that it has acquired a vehicle. The State agency could not simply add that vehicle's fair market or equity value to the values of the household's other vehicles and recompute the household's total resources. The State agency would need to know if the household still had other vehicles and, if so, their current values. Therefore, the State agency would have to ask the household for the additional information.

If the household's report is complete, the State agency would determine the household's eligibility and calculate its allotment. The calculation procedures for determining eligibility and allotments are the same for MRRB households as they are for the current prospective system. Of course, as discussed earlier, the State agency could determine eligibility prospectively or retrospectively.

In retrospective budgeting, the State agency would use most circumstances from the budget month in calculating the allotment. The State agency would prorate (as described earlier) three types of income: most self-employment income, contract income, and some forms of educational grants. The State agency would have the option of converting any stable income which the household receives weekly or every two weeks to regular monthly amounts. The Department is also giving State agencies an option concerning the public assistance (AFDC) grant. In calculating the allotments, the State agency may use either the grant that the household received in the budget month or the grant the household will receive in the issuance month. The household will be able to deduct its expenses from the budget month. If shelter expenses are billed less often than monthly, the household may choose to have them averaged over the certification period. After calculating the allotment, the State agency will issue it to each eligible household and explain to the household how the agency derived the allotment.

The proposed rule of December 5, 1980, included provisions regarding proration of income which are the same as those contained in these rules. Subsections (5)(f)(1) (A) and (B) of the Act require proration for certain categories of households. Allowing proration in these cases will moderate the extreme fluctuations in circumstances which these households experience. However, State agencies may request a waiver of this requirement as allowed in section 5(f) of the Act. It should be noted that AFDC regulations now permit proration (See 45 CFR 233.20(a)(3)(iii)).

*Verification*

In the proposed rule, the Department set forth verification requirements that closely resembled what is now required when a household reports a change. The proposed requirements would have mandated the verification of earned income, actual utility costs, medical expenses, unearned income (which has changed by more than $25) and residency. A State would require a household to verify household composition and citizenship only if the information appeared "questionable." In addition, a State agency would exercise discretion in verifying liquid resources and loans, continuing shelter changes, entitlement to a utility standard, household size, and factors identified by an error-prone profile.

The comments on the proposal were varied. Some recommended the verification of only questionable information, some commentors wanted all information verified, and some thought that only significant changes in some factors, such as medical or utility expenses, should be verified.

For use in MRRB, the Department has adopted requirements designed to ensure that critical benefit determination factors are verified each month. The requirements also extend greater flexibility to State agencies in electing to require verification of other factors. This flexibility will allow State agencies to establish procedures consistent with their own systems and with the requirements of the Aid to Families with Dependent Children program.

The verification requirements included in this rule for information submitted in monthly reports are as follow: (1) Each month households are required to verify gross nonexempt income, utility expenses which exceed the standard utility allowance, medical expenses, and any reported information which the State agency determines is questionable. (2) When information has changed since the previous report (that is, during the budget month), the household must verify alien status, social security numbers, residency, and citizenship. (3) The State agency is allowed to require the household to verify any other information on the monthly report.

These interim rules differ from the proposed rules in three significant ways. The first difference is that in the interim rules all income must be verified. This change simplifies the rules by treating all nonexempt income alike: it all must be verified each month. The second difference is that the interim rules require that all questionable information must be verified, not just questionable household composition and citizenship. This change serves the Department's objective of ensuring program integrity. Finally, this interim rule extends administrative flexibility by allowing the State agency to require verification of any of the other information included in the monthly report. No list of factors which may be verified or conditions which must be extant is included.

These changes are consistent with proposed changes included in proposed rules published in the **Federal Register** of April 2, 1982, at 46 FR 14160. Those proposed rules deal with requirements for verification at the time of certification.

These interim rules also provide that if claimed medical expenses are not verified the household would not be given a deduction for those medical expenses. This approach protects the integrity of the food stamp processing system and yet allows households to participate based on the information which they can verify. This same approach is used regarding utility expenses except that where a household does not verify utility costs the State agency shall allow the utility standard if the household is entitled to that standard.

Also, any reported increases in income or other changes which would decrease benefits, but are not verified, will still be processed. Households which report changes that decrease benefits (for example, significant increases in income) should not be allowed to receive a higher amount of benefits solely because they failed to verify those changes. If that were the case, there would simply be no incentive to verify those changes.

*Incomplete Filing*

Under the proposed rule, a State agency would have been required to give a household an extension period if it filed an incomplete report or did not file by the specified filing date. Some State agencies did not like the extension period. They indicated that it would be preferable to terminate the participation of any household which failed to file properly. In the event a household later complied reinstatement would be possible.

In this interim rule the Department has retained certain requirements regarding incomplete filing. Section 6(c)(2) of the Act requires the Department to offer households an extended filing period. If a State agency were to terminate nonfiling households routinely, it is probable that many households would leave the program. An extension period allows the household to remain in the program and should result in a reduced number of new applicants. An extension period is also useful for a household which, because of an emergency or other circumstances beyond its control, is late either in reporting or in providing required verification.

As in the proposal, these interim rules provide that if a household does not file its complete monthly report by its initial filing date, the State agency must notify the household within five days. The notice must tell the household exactly what is missing, when the household must return the completed form, and must offer the household assistance in submitting a complete report. The household must be allowed at least ten days from the mailing date of the reminder notice to submit a complete report.

In the event a household does not provide required verification the State agency has a number of different courses of action to take depending upon what information is unverified. If earned income is unverified, the report is incomplete. The State agency must give the household ten additional days beyond the initial filing date to verify the change. If the income remains unverified, the State agency must terminate the household. If medical expenses are unverified, the household will not receive the medical deduction.

If the household does not verify anything else which is required, the State agency will act on the unverified information if it would decrease the allotment, and will not act on the unverified information if it would increase the household's allotment. The Department proposed this procedure in its December 5, 1980 rulemaking on this subject. By using this procedure, a State agency can process reports in more cases and timely issue more allotments.

**Issuance of Benefits**

*Timely Issuance*

The proposed rule would have required State agencies to issue benefits within thirty days of the end of the budget month. Under that proposal, FNS could have approved a longer time limit for State agencies which could not meet the one month deadline because of a longer time period for AFDC issuance, or because of the Food Stamp Program's "staggering requirements" for mail issuance. Those mail issuance rules provide that a State agency may mail benefits on different dates up until the fifteenth day of the next month.

The commenters took various positions on this provision. Some wanted all issuances to be made within thirty days of the end of the budget month. They hoped to minimize the time lag between a household's need situation and the delivery of assistance specifically calculated to meet that need. Other commenters wanted FNS to suspend the rules on staggering so that State agencies could issue benefits at any time within the first month following the budget month. Some wanted the choice between the thirty and forty-five day systems to be left completely to the State agencies.

The interim rules take into account the development of the one and two month MRRB systems, as described earlier in this preamble. The interim rules for a one-month system require that, if the household files a complete report by its scheduled filing date, the State agency must provide the household with an opportunity to participate within thirty days of the end of the budget month. In a two-month system, the State agency must provide the household with an opportunity to participate within forty-five days after the budget month. An opportunity to participate means that the household must be able to obtain its coupons by the thirtieth or forty-fifth day. It is not sufficient to mail ATP cards on the last day, or even to mail them so that they arrive on the last day of timely issuance. The household must be able to transact its ATP card by the thirtieth or forty-fifth day. In a HIR system (where benefits are issued over the counter at the local food stamp office), the household must be able to obtain its coupons at an issuance office by the thirtieth or forty-fifth day.

*Delayed Issuance*

As previously discussed, the State agency must extend a household's filing date by at least ten days if the household does not file its report by the original filing date. If the household files its report by this extended filing date, the State agency has ten days beyond the normal issuance date to provide an opportunity to participate. For example, a household's normal filing date may be March 5 and its corresponding issuance date may be March 20. If the household's extended filing date is March 15, and the household reports on that date, the State agency must provide an opportunity to participate by March 30. This extension of ten days serves a number of functions. It acts as an incentive to the household to report promptly. It also provides the State agency with the extra time needed to process the report. Finally, the ten-day limit guarantees that households which do comply with the reporting requirements, even if they are late, will not have to wait too long for their benefits.

The single exception to this ten day extended issuance date concerns households in a two month system. If a household files by its extended filing date, it must receive an opportunity to participate within forty-five days of the end of the budget month. For example, the household's filing date may be April 5 and its corresponding issuance date may be May 10. If the household submits a complete report on April 15, the State agency must provide an opportunity to participate by May 15. Although the State agency may extend the household's opportunity to participate, it may not do so beyond the forty-fifth day after the end of the budget month. The forty-fifth day serves as a reasonable issuance deadline for households which file before the extended filing date.

Some households may miss the extended filing date but file before the end of the issuance month. Under these rules, the State agency may choose to reinstate the household by providing it with an opportunity to participate. This reinstatement and opportunity to participate could take place within ten days of the date the complete report is filed, or by the extended issuance date. Once the issuance month has passed, however, a household which has not yet reported has lost its benefits for the issuance month.

**Other Reporting Requirements**

*Households Which File Monthly*

Section 6(c)(3) of the Food Stamp Act states that households which file monthly reports cannot be required to file any other reports of changes. Therefore, the Department is forbidding any additional reporting requirements. State agencies may not impose the current reporting requirements of § 273.12(a) in addition to the monthly reporting requirements.

*Households Which Do Not File Monthly*

As stated earlier, certain households which are subject to retrospective budgeting must be excluded from monthly reporting. These are households whose adult members are all elderly or disabled persons without earned

income. These households must comply with the reporting requirements of § 273.12 (a) and (b). The regulations require these households to report the following changes within ten days: 1) changes in the source of income or in the amount of income of more than $25, except for public assistance grants and some general assistance grants; 2) changes in household composition; 3) changes of residence and the resulting change in shelter cost; 4) acquisition of a nonexcluded licensed vehicle; 5) changes in liquid resources such that they reach $1,500; and 6) changes in deductible medical expenses of more than $25.

*Termination*

If a household's circumstances change sufficiently the State agency may need to suspend or to terminate the household. Suspension is discussed later in this preamble. The State agency will also terminate a household's participation if it does not file a complete monthly report by the extended filing date.

When the State agency terminates a household's participation, the household need not receive advance notice of termination. However, the notice must explain that the household can reinstate its participation by filing its complete monthly report during the issuance month. However, after the issuance month has passed, the household will be unable to reinstate its participation and will have to file a new application. The only exception to this is a termination which results from information from a source other than the monthly reporting system. In that case advance notice must be provided.

*Suspension*

The proposed rule provided that households which became ineligible because of a temporary increase in net income were to be put in a suspended status and were to continue to file reports. The State agency would then reinstate benefits when the household's report indicated eligibility.

Three State agencies opposed suspensions. For example, Nevada stated that "our computer system cannot handle suspending an issuance" and that substantial computer re-programming would be necessary. Another State wanted households to be eligible for program reinstatement for up to thirty days based upon the previous application and a written request for a supplement. Two state agencies favored suspensions, one of which noted that suspensions could be easily programmed and the files quickly reactivated. One legal assistance group and two public interest groups favored the provision since it kept the recipient in the system.

The Department has chosen to make suspension optional for State agencies. The alternatives are suspension (and reinstatement by filing a monthly report) and termination (followed by another application). The State agencies can best judge which system is most appropriate for their caseload and computer system. Thus, to avoid the difficulties of repeated application, the Department is permitting State agencies to suspend issuance to a household which becomes ineligible for one month because of a periodic increase in income from a recurring income source. This could be a situation where the household receives a fifth paycheck in a month where the household usually receives four per month.

If a State agency chooses to suspend a household's issuance it can do so for one month. The household would file an additional monthly report. The agency would continue to process the monthly report and terminate the household if it were ineligible for two months in a row.

If a State agency suspends a household's issuance, it will nonetheless consider the household to be certified. This means that the month following the suspension will not be considered a beginning month, nor would the allotment issued in that month be prorated. In this way, a household whose issuance was suspended can resume its participation without the need for any special adjustments or calculations.

If a State agency does not choose the option of suspending these households, it would instead terminate them. In providing the suspension/termination options, this interim rule responds to State agency comments on the December 5, 1980, proposal. For example, California mentioned that the "AFDC regulations do not require suspension." California recommended an optional system that "would provide State agencies with the flexibility needed to parallel the AFDC system as much as possible." As mentioned earlier, this rule will allow State agencies to choose the method which best meets their needs and capabilities.

**Fair Hearings and Continued Benefits**

*Fair Hearings*

A household which receives food stamps is entitled to a fair hearing if it is aggrieved by an action of the State agency which affects the household's participation. The regulations governing fair hearings in the Food Stamp Program appear at 7 CFR 273.15.

*Continuation of Benefits*

A household which requests a fair hearing also usually receives a continuation of benefits pending the outcome of the hearing, unless the household asks that its benefits not be held constant. Under subsection 11(e)(4) of the Act, households requesting a hearing are entitled to the continuation of benefits until the hearing is completed and an adverse decision rendered or until the household's certification period ends, whichever occurs earlier. As noted above, under retrospective budgeting the Department is not requiring advance notice of reductions and terminations of benefits. Households requesting fair hearings, however, will be promptly (within five working days of receipt by the State agency of the request for the hearing) restored to the level they would have been entitled to receive if the State agency had not taken the contested action. That benefit level would continue until an adverse decision is actually rendered or the household's certification period expires.

Under the prospective budgeting system, the amount of the food stamp allotment is held constant when a fair hearing is timely requested. However, the State agency continues to process reported changes under the current system. In retrospective budgeting the Department is requiring a somewhat different system. Because the household will be submitting reports on a monthly basis, the State agency will hold constant whatever factor of eligibility or benefit level is the subject of the fair hearing. This may or may not result in a continuation of the entire amount of the allotment. For example, if a household appeals a reduction in benefits that was caused by a change in dependent care costs, the State agency would hold the cost steady, but process other changes in income and deductions, and thus adjust the actual allotment as well. In each case, the reason given by the household for requesting the hearing will determine whether it is the entire allotment or a particular factor of the allotment which is held constant.

*Recertification*

These interim rules require that State agencies certify MRRB households at least once every twelve months, but not more frequently than every six months. As discussed earlier under the heading "Certification period," the Department does not possess enough information to allow State agencies to certify households indefinitely. The Department is attempting to integrate the monthly reporting procedure with a

recertification procedure. Therefore, as the Department proposed in its December 5, 1980, rulemaking, there are two options for recertifying monthly reporting households as discussed below.

*Option One: Recertification Form*

Under this option, the State agency would send the household a notice of expiration and a recertification form instead of a monthly report form. The household would then submit the recertification form at the beginning of the last month of its certification period. This recertification form would seek information about the budget month which corresponds to the first month of the new certification period. Unlike the monthly report form, the recertification form would contain questions on all factors of eligibility and allotment levels. If a State agency uses prospective eligibility, the recertification form would also contain questions about the household's future circumstances.

*Option Two: Monthly Report and Addendum*

This option differs from the first option only in that the State agency would send the household a notice of expiration and a regular monthly report, and an addendum, as well. The addendum would obtain all information about the factors of eligibility and the allotment level which the monthly report does not request. For example, the monthly report might not contain questions concerning real property (land and buildings), alien status, and income from educational grants. The addendum would address these matters and others not included in the monthly report. The household would then submit the report form, to the State agency at the beginning of the last month of its certification period and the addendum no later than the interview.

*Interview*

Under either option, the State agency must interview the household. This would be done in accordance with the current food stamp regulations, as contain in 7 CFR 273.14(c)(2). That is, the State agency would interview the household at some time during the last month of its expiring certification period and process the recertification so as not to interrupt the household's issuance schedule. Two commenters on the December 5, 1980, proposed rule suggested a third option which would allow recertification based on the interview alone without an additional form. The Department has decided not to allow this option so that a complete written record of the recipient's statement of circumstances is provided.

*Households Which Do Not Report Monthly*

Some households which have their allotments calculated retrospectively do not file monthly reports. These are households whose adult members are all elderly or disabled individuals without earned income. The State agency will recertify these households in accordance with 7 CFR 273.14, the Food Stamp Program's regulation on recertification. However, in the recertification process the State agency will determine eligibility and calculate the household's allotment in accordance with this rule, 7 CFR 273.21.

**Regulatory Flexibility Analysis**

*Need for Action*

The Omnibus Budget Reconciliation Act of 1981, Public Law 97-35, requires the Department of Agriculture to implement a system of retrospective budgeting and periodic reporting (MRRB) in the Food Stamp Program. This action amends Title 7 of the Code of Federal Regulations for that purpose.

The Department is publishing this rule in interim form for three reasons, as mentioned earlier. The first reason is to fulfill promptly Congress's intent that similar accounting procedures be used in both the Aid to Families with Dependent Children (AFDC) Program and the Food Stamp Program. The second reason is that the Department has already received comments on a similar rule which was proposed on December 5, 1980. The third reason, which relates to making this rule *interim*, is that the Department would like to receive additional comments based upon the operation of MRRB in its current form.

*Justification of Selected Alternatives*

In writing this regulation, the Department identified the following two major problems for which there are alternative solutions. The Department has summarized the problems and alternatives below, and justified the alternative which was selected.

*Prospective Eligibility*

Subsection 5(f) of the Food Stamp Act of 1977, as amended, permits the Department to provide for a prospective determination eligibility for households whose allotments are calculated retrospectively. This means that a State agency could determine eligibility based upon future circumstances but would calculate an allotment based upon past circumstances.

The alternatives were to require prospective eligibility for all households, to forbid it for all households, to designate it for certain households, or to allow State agencies to decide. Prospective eligibility generally reduces the Program's benefit cost by reducing the number of months in which a household is eligible for food stamps. On the other hand, prospective eligibility increases administrative cost for on-going cases by increasing the amount of information which a State agency must obtain and the amount of work it must do to issue an allotment.

No single alternative seemed clearly preferable to the State agencies or to the recipients. The Department has chosen to give State agencies the choice because of the uncertain costs and savings of each choice and the desirability of granting State additional flexibility.

*Frequency of Reporting*

Subsection 6(c) of the Food Stamp Act of 1977, as amended, requires the Department to set standards for the filing of periodic reports by households. The alternatives are to require monthly reports, to require reports filed at different time intervals, or to allow each State agency to set its own frequency of reporting.

Monthly reporting exactly matches the monthly issuance of food stamps, and therefore is simple to use when calculating allotments. The AFDC program also uses monthly reporting. Finally, the Congress clearly presupposed the use of monthly reporting, as shown by both the House and Senate committee reports on this subject. Reporting at a longer interval would reduce the administrative cost of the Program, but could increase the Program's benefit costs. This would occur because of the lag time between the occurrence of a change in its effect on a household's allotment.

The Department has chosen monthly reporting based on the current food stamp and AFDC monthly issuance systems and based on the direction given by Congress in the House and Senate reports.

**List of Subjects**

*7 CFR Part 271*

Administrative practice and procedure, Food stamps, Grant programs-social programs.

*7 CFR Part 272*

Alaska, Civil Rights, Food stamps, Grant programs-social programs, Reporting and recordkeeping requirements.

*7 CFR Part 273*

Administrative practice and procedure, Aliens, Claims, Food stamps, Fraud, Grant programs-social programs, Penalties, Reporting and recordkeeping requirements, Social Security, Students.

**Amendment**

For the reason set out in the preamble, Parts 271, 272, and 273 of Subchapter C, Chapter II of Title 7, Code of Federal Regulations, are amended as set forth below.

## PART 271—GENERAL INFORMATION AND DEFINITIONS

**§ 271.2 [Amended]**

1. In § 271.2, insert the following in alphabetical order:

"Adequate notice" in a Monthly Reporting and Retrospective Budgeting system means a written notice that includes a statement of the action the agency has taken or intends to take; the reason for the intended action; the household's right to request a fair hearing; the name of the person to contact for additional information; the availability of continued benefits; and the liability of the household for any overissuances received while awaiting a fair hearing if the hearing official's decision is adverse to the households. Depending on the timing of a State's system and the timeliness of report submission by participating households, such notice may be received prior to agency action, at the time reduced benefits are received, or, if benefits are terminated, at the time benefits would have been received if they had not been terminated. In all cases, however, participants will be allowed ten days from the mailing date of the notice to contest the agency action and to have benefits restored to their previous level. If the 10-day period ends on a weekend or a holiday and a request is received the day after the weekend or holiday, the State agency shall consider the request to be timely.

"Beginning month(s)" in a Monthly Reporting and Retrospective Budgeting system means either the month in which the household applies for food stamps (where the State agency has adopted a one month accounting system) or the month the household applies for food stamps and the month thereafter (where the State agency has adopted a two month accounting system). Regardless of the above, a beginning month cannot be any month which immediately follows a month in which a household is certified.

"Budget month" in a Monthly Reporting and Retrospective Budgeting system means the fiscal or calendar month from which the State agency uses income and other circumstances of the household to calculate the household's food stamp allotment for the corresponding issuance month.

"Issuance month" in a Monthly Reporting and Retrospective Budgeting system means the fiscal or calendar month for which the State agency shall issue a food stamp allotment. Issuance is based upon income and circumstances in the corresponding budget month. In prospective budgeting, the budget month and issuance month are the same. In retrospective budgeting, the issuance month follows the budget month and the issuance month shall begin within 32 days after the end of the budget month.

"Prospective budgeting" in a Monthly Reporting and Retrospective Budgeting system means the computation of a household's food stamp allotment for an issuance month based on an estimate of income and circumstances which will exist in that month.

"Retrospective budgeting" in a Monthly Reporting and Retrospective Budgeting system means the computation of a household's food stamp allotment for an issuance month based on actual income and circumstances which existed in a previous month, the "budget month."

## PART 272—REQUIREMENTS FOR PARTICIPATING STATE AGENCIES

2. In § 272.1, paragraph (g)(36) is added to read as follows:

**§ 272.1 General terms and conditions.**

* * * * *

(g) *Implementation.* * * *

(36) Amendment 184. State agencies may implement this Monthly Reporting and Retrospective Budgeting rule at any time, but shall implement this rule State-wide no later than October 1, 1983. Prior to October 1, 1983, this rule may be implemented State-wide, in only part of a State (such as in certain project areas), or for only certain reasonable classifications of households (such as for only households receiving Aid to Families with Dependent Children) so long as the implementation is State-wide by October 1, 1983. State agencies shall send monthly reports to households so that they can report their October, 1983 circumstances in accordance with § 273.21(h). Before implementing this rule, each State agency shall obtain the approval of the Food and Nutrition Service (FNS), in accordance with the following requirements.

(i) To obtain the approval of FNS, the State agency shall submit the results of a pretest of its Monthly Reporting and Retrospective Budgeting (MRRB) system. The pretest shall demonstrate:

(A) The participating household's ability to understand and complete the monthly reporting form; and

(B) The State agency's ability to process the monthly report's information and to issue accurate and timely allotments.

(ii) If a State agency has operated a MRRB system in its Aid to Families with Dependent Children (AFDC) Program, and the State agency can demonstrate that its system meets the requirements of this paragraph, FNS may waive the pretest.

(iii) Unless otherwise specified in § 273.21 of this chapter, all other food stamp regulations shall apply to State agencies and to applying or participating households.

* * * * *

3. In § 272.3, paragraph (c) is revised by adding a new paragraph (7) to read as follows:

**§ 272.3 Operating guidelines and forms.**

* * * * *

(c) *Waivers.* * * *

(7) Notwithstanding the preceding paragraphs, waivers may be granted by the Administrator of the Food and Nutrition Service or the Deputy Administrator for Family Nutrition Programs as provided in section 5(f) of the Act. Waivers authorized by this paragraph are not subject to the public comment provisions of § 272.3(d).

## PART 273—CERTIFICATION OF ELIGIBLE HOUSEHOLDS

4. In Part 273, new § 273.21 is added to read as follows:

**§ 273.21 Monthly Reporting and Retrospective Budgeting (MRRB).**

(a) *Choice of options.* In choosing between a one-month and a two-month MRRB system, and in choosing between prospective and retrospective determination of eligibility the State agency shall choose the option which is more consistent with its AFDC–MRRB system. The State agency shall choose a less consistent option only if FNS grants a waiver.

(b) *Included and excluded households.* This section provides for an MRRB system for determining household eligibility and benefits. This system is an alternative to the prospective budgeting system provided in the preceding sections of this part. An MRRB system shall include all households except as follows:

(1) *Retrospective budgeting.* The State agency shall exclude migrant farmworker households from

retrospective budgeting as long as the households are in the migrant job stream.

(2) *Monthly reporting.* (i) The State agency shall exclude from monthly reporting the following households:

(A) Migrant farmworker households while they are excluded from retrospective budgeting; and

(B) Households whose members are all without earned income and are at least sixty years old or receive Supplemental Security Income (SSI) benefits under title XVI of the Social Security Act or disability and blindness payments under titles I, II, X, XIV, and XVI of the Social Security Act.

(ii) The State agency may exclude from monthly reporting households whose adult members are all without earned income and are at least sixty years old or receive Supplemental Security Income (SSI) benefits under title XVI of the Social Security Act or disability and blindness payments under titles I, II, X, XIV, and XVI of the Social Security Act, unless these households file AFDC monthly reports.

(3) *Special assistance.* The State agency shall provide special assistance in completing and filing monthly reports to households whose adult members are all either mentally or physically handicapped or lacking in reading and writing skills such that they cannot complete and file the required reports.

(4) *Certification period.* The household shall be certified for a continuous period of up to twelve months, but for no less than six months.

(c) *Information on MRRB.* At the certification interview, the State agency shall provide the household with the following:

(1) An oral explanation of the purpose of MRRB;

(2) A copy of the monthly report and an explanation of how to complete and file it;

(3) An explanation of what the household shall verify when it submits a monthly report and how it will verify it;

(4) The telephone number (toll free for households outside the local calling area) which the household may call to ask questions or to obtain help in completing the monthly report; and

(5) Written explanations of this information.

(d) *One and two-month systems.* Each State agency shall adopt either a one-month or a two-month MRRB system. A one month system shall have one beginning month in each certification period and a two-month system shall have two beginning months. However, the State agency shall not consider as a beginning month any month which immediately follows a month in which a household is certified.

(1) *One-month system.* In the one-month system, the issuance month immediately follows its corresponding budget month. There is one beginning month of participation in this system, the month of application. The month preceding application shall be the first budget month.

(2) *Two-month system.* In the two-month system, the issuance month is the second month following its corresponding budget month. There are two beginning months of participation in this system, the month of application and the following month.

(e) *Determining eligibility and allotments in the beginning months for households suffering serious hardship.* The State agency shall use the special procedures (prospective budgeting) of this paragraph only for households who would experience serious hardship if the State agency used the budgeting procedures described in paragraphs (f) and (g) of this section. (For all other households, the State agency shall use the procedures in paragraphs (f) and (g) of this section).

(1) *Households which suffer serious hardship.* A household suffers serious hardship from retrospective budgeting if:

(i) It has gained or expects to gain a new household member in the month of application; or

(ii) It is entitled to expedited service, determined prospectively, for the month of application, in accordance with § 273.2(i); or

(iii) It would otherwise experience a serious hardship as defined by the State agency; provided that

(iv) The household has not deliberately caused a reduction in its own income through participation in a strike, quitting a job, or reducing its wages; and

(v) The household's income has not been reduced to recover prior overpayments in assistance programs such as, but not limited to, Supplemental Security Income (SSI), Aid to Families with Dependent Children (AFDC) and General Assistance (GA).

(2) *Determining eligibility for serious hardship cases.* The State agency shall determine eligibility prospectively in the beginning month(s).

(3) *Calculating allotments for serious hardship cases.* The State agency shall calculate allotments prospectively in the beginning month(s).

(4) *The first month of retrospective budgeting for serious hardship cases.* The State agency shall begin to base issuances to the household on retrospective budgeting during the first month for which the State's system can use the month of application as a budget month. In a one-month system, the first month for which the issuance is based on retrospective budgeting shall be the second month of participation. In a two-month system, the first month for which the issuance is based on retrospective budgeting shall be the third month of participation. For the purposes of this paragraph any income that the household received in the month of application from a source which no longer provides income to the household (income from a terminated source) shall be disregarded.

(f) *Determining eligibility for households not certified under the serious hardship provisions of § 273.21(e).* The State agency shall determine eligibility in accordance with either of the following options:

(1) *Prospective eligibility.* The State agency shall determine eligibility by considering all factors of eligibility prospectively for each of the issuance months.

(2) *Retrospective eligibility.* The State agency shall determine eligibility by considering all factors of eligibility retrospectively using the appropriate budget month.

(g) *Calculating allotments for households not suffering serious hardship.*—(1) *Household composition.* (i) If eligibility is determined retrospectively the State agency shall determine the household's composition as of the last day of the budget month.

(ii) If eligibility is determined prospectively (such as for serious hardship cases or households processed under paragraph (f)(1) of this section), the State agency shall determine the household's composition as of the issuance month.

(iii) In a two-month system, if the household gains a member in the month between the budget month and the issuance month, the State agency shall determine eligibility using the household's composition during the issuance month.

(2) *Income and deductions.* For the household members as determined in accordance with paragraph (g)(1) of this section, the State agency shall calculate the allotment using the household members' income and deductions from the budget month, except as follows:

(i) The State agency shall annualize self-employment income which is received other than monthly, in accordance with § 273.11(a).

(ii) The State agency shall prorate income received by contract in less than one year over the period the income is

intended to cover, in accordance with § 273.10(c)(3)(ii).

(iii) The State agency shall prorate nonexcluded scholarships, deferred educational loans, and other educational grants over the period they are intended to cover, in accordance with § 273.10(c)(3)(iii).

(h) *The monthly report form.*—(1) *General.* (i) The State agency shall require each household in the MRRB system to report on household circumstances on a monthly basis as a condition of continuing eligibility.

(ii) The State agency shall provide an individual or agency unit which a household may contact to receive prompt answers about the completion of the form. A telephone number (toll free for households outside the local calling area) which a household may use to obtain further information shall also be available.

(2) *Monthly report form.* The State agency's monthly report form shall meet the following requirements:

(i) Be written in clear, simple language;

(ii) Meet the bilingual requirements described in § 272.4(c) of this chapter;

(iii) Specify the date by which the agency must receive the form and the consequences of a late or incomplete form, including whether the State agency shall delay payment if the form is not received by the specified date;

(iv) Specify the verification which the household must submit with the form, in accordance with § 273.21(j)(2);

(v) Identify the individual or agency unit available to assist in completing the form;

(vi) Include a statement to be signed by a member of the household, indicating his or her understanding that the provided information may result in changes in the level of benefits, including reduction and termination;

(vii) Advise the household of its rights to:

(A) Request a fair hearing based on any decrease or termination of benefits;

(B) File a complete, signed monthly report to be reinstated.

(viii) Include, in prominent and boldface lettering, an understandable description of the Act's civil and criminal penalties for fraud.

(ix) Include a statement of the State agency's authority to require Social Security numbers (SSN's) (including the statutory citation, the title of the statute, and the fact that providing SSN's is mandatory), the purpose of requiring SSN's, the routine uses for SSN's, and the effect of not providing SSN's.

(3) *Reported information.* The State agency shall require, and the household shall report on a monthly basis, the following information about the household:

(i) Budget month income, deductions, household composition, and other circumstances relevant to the amount of the food stamp allotment.

(ii) Any changes in income, deductions, resources or other relevant circumstances affecting eligibility which the household expects to occur in the current month or in future months, or which occurred in the budget month.

(iii) If the State agency uses a combined monthly report for food stamps and AFDC, the State agency shall clearly indicate on the form that non-AFDC food stamp households need not provide AFDC-only information.

(i) *Submitting the monthly report form.* The State agency shall give the household a reasonable period of time after the close of the budget month to submit the monthly reports.

(j) *State agency action on reports.*—(1) *Processing.* Upon receiving a monthly report, the State agency shall:

(i) Review the report to ensure accuracy and completeness.

(ii) Consider the report incomplete only if:

(A) It is not signed by the head of the household, an authorized representative or a responsible member of the household;

(B) It is not accompanied by verification of reported earned income; or

(C) It omits information necessary either to determine the household's eligibility or to compute the household's level of food stamp benefits.

(iii) Determine those items which will require additional verification, in accordance with paragraph (j)(2) of this section.

(iv) Contact the household directly, as needed, to obtain further information on specific items. These items include:

(A) The effect of a reported change in resources on a household's total resources; and

(B) The effect of a reported change in household composition on the applicability of the work registration requirement.

(v) Notify the household, in accordance with paragraph (j)(4)(ii) of this section, of the need to submit a report, correct an incomplete or inaccurate report, or submit the necessary verification within the extension period.

(vi) Determine the household's eligibility by considering all factors, including income in accordance with paragraphs (e) or (f) of this section.

(vii) Determine the household's level of benefits in accordance with § 273.10(e) based on the household composition determined in accordance with paragraph (g)(1) of this section. For those household members the following (except as provided in paragraph (g)(2) of this section) income and deductions shall be considered:

(A) Earned and unearned income received in the corresponding budget month or that has been averaged for the corresponding budget month. The State agency has the option of converting to a regular monthly amount the income that a household receives weekly or biweekly;

(B) The public assistance (PA) grant issued in the corresponding budget month or the PA grant to be issued in the issuance month;

(C) Deductions as billed or averaged from the corresponding budget month, including those shelter costs billed less often than monthly which the household has chosen to average;

(viii) Issue benefits in accordance with Part 274 of this chapter and on the time schedule set forth in paragraph (k) of this section.

(ix) Provide specific information on how the State agency calculated the benefit level, either with the issuance or in a separate notification.

(2) *Verification.* The State agency shall require the household to verify information on the monthly report as follows:

(i) Each month the household shall verify gross nonexempt income, utility expenses which exceed the standard, medical expenses, and all questionable information.

(ii) The household shall verify alien status, social security numbers, residency, and citizenship, if these items have changed since the last report.

(iii) The State agency may require the household to verify any other information on the monthly report.

(3) *Notices.* (i) All notices regarding changes in a household's benefits shall meet the definition of adequate notice as defined in § 271.2.

(ii) The State ageny shall notify a household of any change from its prior benefit level and the basis for its determination. If the State agency reduces or terminates benefits, it shall send the notice so the household receives it no later than either the date the resulting benefits are to be received or in place of the benefits.

(4) *Incomplete filing.* (i) If a household fails to file a monthly report, or files an incomplete report, by the specified filing date, the State agency shall give the household at least ten more days, from the date the State agency mails the notice to file a complete monthly report.

(ii) The State agency shall notify the household within five days of the filing date:

(A) That the monthly report is either overdue or incomplete.

(B) What the household must do to complete the form;

(C) What the extended filing date is;

(D) That the State agency will assist the household in completing the report.

(iii) If a household does not provide required verification, the State agency shall take the following actions:

(A) If the household does not verify earned income, the State agency shall regard the household's report as incomplete, take action in accordance with paragraphs (i)(4)(i) and (i)(4)(ii) of this section and, if appropriate, terminate the household in accordance with paragraph (m) of this section;

(B) If the household does not verify utility expenses in excess of the standard, the State agency shall allow the utility standard if the household is entitled to it;

(C) If the household does not verify medical expenses, the State agency shall not allow a deduction;

(D) If the household does not verify other items for which verification is required, the State agency shall.

(*1*) Act on the reported change if it would decrease benefits.

(*2*) Not act on the reported change if it would increase benefits.

(k) *Issuance of benefits*—(1) *Timely issuance.* (i) The State agency shall provide an opportunity to participate, within either 30 days or 45 days of the end of the budget month, to an eligible household which has filed a complete monthly report by the scheduled filing date.

(ii) The State agency shall provide each household with an issuance cycle so that the household receives its benefits at about the same time each month and has an opportunity to participate before the end of each issuance month.

(2) *Delayed issuance.* (i) If an eligible household files a complete monthly report during its extension period, the State agency shall provide it with an opportunity to participate no later than ten days after its normal issuance date, but in no event later than the 45th day following the end of the budget month.

(ii) If an eligible household which has been terminated for failure to file a complete report files a complete report after its extended filing date, but before the end of the issuance month, the State agency may choose to reinstate the household, by providing it with an opportunity to participate.

(iii) If an eligible household files a complete report after the issuance month, the State agency shall not provide the household with an opportunity to participate for that month.

(l) *Other reporting requirements.*—(1) *Households which file monthly reports.* The State agency shall not require these households to submit any reports of changes other than the monthly reports which paragraph (h) of this section requires.

(2) *Households excluded from monthly reporting.* Households which are excluded from monthly reporting by paragraph (b)(2) of this section shall report changes in accordance with § 273.12.

(m) *Termination.* (1) The State agency shall terminate a household's food stamp participation if the household:

(i) Is ineligible for food stamps, unless suspended in accordance with paragraph (n) of this section;

(ii) Fails to file a complete report by the extended filing date; or

(iii) Fails to comply with a nonfinancial eligibility requirements, such as registering for employment.

(2) The State agency shall issue a notice to the household which:

(i) Complies with the requirements of § 271.2;

(ii) Informs the household of the reason for its termination;

(iii) Explains how the household may be reinstated;

(iv) Informs the household of its rights to request a fair hearing and to receive continued benefits.

(3) The State agency shall issue the notice to the household so that it receives the notice no later than the household's normal or extended issuance date.

(n) *Suspension.* The State agency may suspend a household's issuance in accordance with this paragraph. If the State agency does not choose this option, it shall instead terminate households in accordance with paragraph (m) of this section.

(1) The State agency may suspend a household's issuance for one month if the household becomes temporarily ineligible due to a periodic increase in recurring income.

(2) The State agency shall continue to supply monthly reports to the household for one month.

(3) If the suspended household again becomes eligible, the State agency shall issue benefits on the household's normal issuance date.

(4) If the suspended household does not become eligible after one month, the State agency shall terminate the household.

(o) *Fair hearings.*—(1) *Entitlement.* All households participating in a MRRB system shall be entitled to fair hearings in accordance with § 273.15.

(2) *Continuation of benefits.* (i) Any household which requests a fair hearing and does not waive continuation of benefits shall have its benefits continued until the end of the certification period or the resolution of the fair hearing, whichever is first.

(ii) The State agency shall provide continued benefits no later than five working days from the day it receives the household's request.

(iii) A household whose benefits have been continued shall file monthly reports until the end of the certification period.

(iv) During the fair hearing period the State agency shall adjust allotments to take into account reported changes, except for the factor(s) on which the fair hearing is based.

(p) *Recertification.*—(1) *Timeliness.* The State agency shall recertify an eligible household which timely reapplies and provide it with an opportunity to participate in the household's normal issuance cycle.

(2) *Retrospective recertification.* (i) The State agency shall recertify the household using the information from the corresponding budget month to determine the household's benefit level for the first month of the new certification period.

(ii) If the State agency is operating a two-month MRRB system, the State agency may delay reflecting information from the recertification interview in the household's eligibility and benefit level until the second month of the new certification period.

(iii) The State agency shall recertify households according to one of the two options set forth in paragraphs (p)(3) and (4) of this section.

(3) *Option One: Recertification form.* (i) The State agency shall provide each household with a recertification form to obtain all necessary information about the household's circumstances for the budget month.

(ii) The State agency shall mail the form to the household, along with a notice of expiration, in place of the monthly report form.

(iii) The household shall submit the form to the State agency in accordance with paragraph (h) of this section.

(4) *Option Two: Monthly report and addendum.* (i) The State agency shall provide each household with a notice of expiration and monthly report form and an addendum to obtain all additional information necessary for recertification.

(ii) The State agency shall mail the monthly report form to the household along with the notice of expiration.

(iii) The household shall submit the monthly report to the State agency in accordance with paragraph (i)(1) of this section.

(iv) The State agency shall deliver the recertification addendum to the household along with the monthly report form or obtain the necessary information from the household at the interview.

(v) The household shall submit the addendum to the State agency no later than the time of the interview.

(5) *Interview.* (i) The State agency shall conduct a complete interview with a household member or an authorized representative.

(ii) The State agency shall schedule the interview at any time during the last month of the old certification period.

(iii) If the State agency schedules the interview for a date on or before the normal filing due date of the monthly report, the State agency shall permit the household member and authorized representative to bring the recertification form or monthly report to the interview.

* * * * *

(91 Stat. 958 (7 U.S.C. 2011–2029))

(Catalogue of Federal Domestic Assistance Programs No. 10.551, Food Stamps)

Dated: May 18, 1982.

**Mary Jarratt,**

*Assistant Secretary.*

[FR Doc. 82–14088 Filed 5–24–82; 8:45 am]

BILLING CODE 3410–30–M

federal register

Tuesday
May 25, 1982

Part IV

# Department of Agriculture

## Food and Nutrition Service

**Determining Eligibility for Free and Reduced Price Meals and Free Milk in Schools; Revised Application Procedures and Verification of Eligibility; Proposed Rules**

**DEPARTMENT OF AGRICULTURE**

**Food and Nutrition Service**

**7 CFR Part 245**

## Determining Eligibility for Free and Reduced Price Meals and Free Milk in Schools; Revised Application Procedures

**AGENCY:** Food and Nutrition Service, USDA.

**ACTION:** Proposed rule.

**SUMMARY:** This proposed rule would implement the following changes required by the Omnibus Budget Reconciliation Act of 1981 (Pub. L. 97–35): (1) Require additional information on applications for free and reduced price benefits in the National School Lunch, Commodity School, School Breakfast and Special Milk Programs; (2) require schools to include in their letters to parents only the *reduced price* Income Eligibility Guidelines for meals (schools participating only in the Special Milk Program must include the *free* Guidelines and public releases would still contain both Guidelines); (3) require schools to distribute applications to parents of children in attendance at school; and (4) remove both the hardship and standard deductions and the restriction that School Food Authorities may verify the information on the application solely "for cause". This rule will reduce program abuse and will result in a savings of Federal funds.

**DATE:** To be assured of consideration comments must be postmarked on or before June 24, 1982. Since this proposal is one of two proposals regarding the provisions of section 803 of Pub. L. 97–35, commentors should clearly indicate that comments reference the proposed rule "Revised Application Procedures".

**ADDRESSES:** Comments should be sent to Stanley C. Garnett, Branch Chief, Policy and Program Development Branch, School Programs Division, Food and Nutrition Service, USDA, Alexandria, Virginia 22302. All written submissions will be available for public inspection in Room 509, 3101 Park Center Drive, Alexandria, Virginia 22302, during regular business hours (8:30 a.m. to 5:00), Monday through Friday.

**FOR FURTHER INFORMATION CONTACT:** Stanley C. Garnett, at the address listed above.

**SUPPLEMENTARY INFORMATION:**

### Classification

This proposed action has been reviewed under Executive Order 12291 and has been classified *not major.* We do not anticipate that this proposal will have an impact on the economy of more than $100 million. The proposed rule is intended to ensure that free and reduced price benefits are directed to only those children from families whose income fall within the Income Eligibility guidelines set forth by the Department by household size. No major increase in cost or prices for program participants; individual industries; Federal, State or local government agencies; or geographic regions is anticipated. This proposal is not expected to have significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or foreign markets.

This proposal has also been reviewed with regard to the requirements of Pub. L. 96–354, the Regulatory Flexibility Act. Samuel J. Cornelius, Administrator of the Food and Nutrition Service, has certified that this proposed rule does not have a significant economic impact on State agencies and local School Food Authorities.

In accordance with the Paperwork Reduction Act of 1980 (Pub. L. 96–511), the reporting and recordkeeping requirements contained in this proposed rule will be submitted to the Office of Management and Budget for approval. They are not effective until OMB approval has been obtained.

Samuel J. Cornelius has determined that an urgent need exists to limit the comment period to 30 days since the provisions of this rule directly affect the application process for school year 1982–83. Most States and School Food Authorities print their applications during the summer months in order to have applications prepared for the start of the school year in August or September. In order to meet these timeframes, an interim rule must be in place no later than July, thus necessitating the short comment period. The Department intends to solicit additional public comment on the forthcoming interim rule which will be effective for School Year 1982–83.

### Background

Section 9 of the National School Lunch Act (Act) contains a provision that lunches be served free or at a reduced price to children who are unable to pay the full price of a lunch. Prior to Pub. L. 97–35, local school officials were required to determine eligibility for free and reduced price meals "solely on the basis of an affidavit executed in such form as the Secretary may prescribe by an adult member of such household." Regulations implementing section 9 require that the affidavit (application) request only that information necessary to determine eligibility, namely family size and family income. In order to determine eligibility school officials were directed to compare the Income Eligibility Guidelines issued by the Secretary to the family size and income information furnished by the parent.

Previously, section 9 of the Act also provided that school officials "may for cause seek verification of the data in such application." The "for cause" provision limited verification to those situations where school officials had actual cause to believe the information on the application was erroneous.

### Changes Due to Public Law 97–35

In an effort to control Federal spending, curtail abuse, and direct Federal benefits to the most needy, Congress made fundamental changes in the child nutrition programs. Many of these changes affect the free and reduced price application process. Section 803 of the Omnibus Budget Reconcilation Act of 1981 (Pub. L. 97–35) amended section 9 of the National School Lunch Act (Act) to implement these changes. These changes require:

(1) The applicant to furnish the social security numbers of all adult household members on the free and reduced price application;

(2) Appropriate documentation of income or documentation showing that the household is participating in the Food Stamp Program;

(3) Only the reduced price guidelines be included in the letter to parents with an explanation that households with income less than or equal to the reduced price guidelines are eligible for either free or reduced price meals;

(4) Schools to distribute applications to the parents of children in attendance at school;

(5) The elimination of hardship provisions and standard deductions;

(6) The elimination of the restriction that allowed verification by School Food Authorities solely "for cause";

(7) The Department to conduct a pilot study on income verification; and

(8) That the household's annual income at the time of application be considered in the eligibility determination.

### Departmental Response

In response to the provisions of section 803, Pub. L. 97–35, the Department is publishing two proposed rules.

This proposal, Revised Application Procedures, is primarily intended to

address those provisions of section 803 affecting the application process at the beginning of the school year. Many of these provisions are nondiscretionary. Normally the Department would publish nondiscretionary provisions as a final rule since public comment is unnecessary. However, this rule contains several ancillary provisions which are subject to Departmental discretion. For this reason, the Department intends to provide a 30-day comment period. This will enable the Department to analyze the comments and publish an interim rule in sufficient time to affect the 1982–83 application process.

The second proposal, Verification of Eligibility, is designed to address the verification-related provisions of section 803. A 60-day public comment period will be provided. Based on an analysis of public comments, the Department intends to set forth an interim rule early next school year for implementation during the school year.

Comments will be accepted for both interim rules. One final rule incorporating all provisions of section 803, Pub. L. 97–35 will be developed following an analysis of comments received.

This Proposed rule will implement the following changes to the free and reduced price application process in response to section 803 as follows: (Comments are solicited on those areas where the Department is able to make revisions, as described at the end of the preamble.)

(1) *Requires additional information on free and reduced price applications.* This rule proposes to revise Part 245 to expand the information required on the free and reduced price application. As required by section 803 of Pub. L. 97–35, the applicant must provide the social security numbers of all adult household members in order for the application to be considered for benefits. For purposing to define "adult" as an individual who is 21 years of age or older. Further, the Department proposes to define "household" as "family" (§ 245.2(b)).

To reduce program abuse, section 803(b) also amended section 9 of the Act to require the Secretary to prescribe adequate documentation of eligibility for benefits. The Department proposes to define documentation as completion of the following information on the application: (1) Total household income; (2) names of all household members; (3) social security numbers of all adult household members, or an indication that application for one has been made or in the case of aliens ineligible for social security numbers, an indication that none can be acquired; and (4) signature of the parent or legal guardian. This approach is intended to maintain the existing application process, thus limiting the burden on the applicant as well as on the school official. These are Federal minimums; State agencies and local School Food Authorities may require households to provide additonal information to establish eligibility for free and reduced price benefits. This proposed rule would further expand the information required on the application by including a question regarding household participation in the Food Stamp Program. This will assist in the verification process as explained in the proposed rule, Verification of Eligibility.

These provisions will affect the first performance standard of the Assessment, Improvement, and Monitoring System (AIMS). That standard requires that each child's application for free and reduced price benefits is correctly approved or denied. Prior to Pub. L. 97–35, applications were deemed complete if the total number of family members, total family income, and the parent's or guardian's signature were provided. This proposal would change the requirements for a complete application to include: (1) Social security information; (2) total household income; (3) names of all household members; and (4) the signature of the parent or legal guardian.

Commentors should be aware that the provision of information required on a free and reduced price application would be considered a condition of eligibility, as required by Pub. L. 97–35. As a result, State agencies must ensure that all School Food Authorities obtain the information prescribed by the Secretary. Applications which do not contain such information will be considered incomplete and therefore insufficient to substantiate the receipt of Federal funds. The State agency or School Food Authority must also deny benefits if the information on the application establishes ineligibility or is incomplete, and shall not claim special assistance reimbursement based on such application. The School Food Authority must notify the household in writing of a denial of benefits. The notice must advise the household of the denial and of the right to a fair hearing. The reasons for ineligibility must be properly documented and must be retained on file at the School Food Authority.

Section 7 of the Privacy Act of 1974 requires any Federal, State, or local government agency which requests an individual to disclose his or her social security number, to inform the individual whether the disclosure is mandatory or voluntary, by what authority the number is solicited, and what uses will be made of it. In this regard, the Department's Office of Inspector General intends to use social security numbers to verify income information on a sample of applications. In order to comply with section 7, the application for free and reduced price benefits must indicate that section 9 of the National School Lunch Act, as amended, requires the social security numbers of all adult household members as a condition of eligibility. In addition, the application must indicate that the social security number(s) may be used to verify the information on the application and that failure to provide the required social security information will lead to the denial of benefits.

Under this proposal, the letter or notice to parents must indicate that a completed application is a condition of eligibility for free and reduced price meals. In addition, the letter to parents must indicate that all households with children receiving free and reduced price benefits must notify the appropriate school officials of changes in household size or increases in income of over $25 per month.

(2) *Requires schools to include in their letter to parents only the reduced price Income Eligibility Guidelines,* and an explanation that households with income equal to or less than the reduced price guidelines are eligible for either free or reduced price meals. Schools participating in the Special Milk Program, where the School Food Authority exercises its option to serve free milk, must send home the free Guidelines. Public releases would continue to contain both Guidelines.

(3) *Requires schools to distribute applications to parents of children in attendance at school.* Existing program regulations already require schools to distribute applications to parents of children in attendance at school. At School Food Authority discretion, applications may be mailed or handed out in classrooms and carried home by students.

(4) *Eliminates the hardship provisions and standard deductions.* From 1973 until the passage of Pub. L. 96–499, the Department allowed a family to deduct from its stated income the cost of certain "hardships" that the family could not reasonably anticipate or control. Last school year, Pub. L. 96–499 established a standard deduction to offset the removal of hardship deductions. This school year, section 803 of Pub. L. 97–35 permanently removes both hardship provisions and standard deductions.

(5) *Eliminates the "for cause" restriction.* State agencies and School Food Authorities are now authorized under section 9(b)(2)(C) of the Act, as amended, to verify the information on the application at their discretion.The Department proposes that State agencies or School Food Authorities doing so must ensure that verification is applied without regard to race, sex, color, national origin, age or handicap. In today's **Federal Register**, the Department proposes the "Verification of Eligibility" rule to implement several verification related provisions of section 803. That proposal sets forth the Department's requirements concerning the verification of information on the application, notification of adverse action, and continuation of benefits.

(6) *Exempts pilot projects.* Section 803 of Pub. L. 97-35 also requires the Department to conduct a pilot study on verification. Schools that participate in that study will be instructed by the Department on the use of specific application forms, documentation, and techniques for verification of eligibility information.

The pilot study will utilize several different application and verification methods starting this school year. The available results of the pilot study will be carefully evaluated by the Department and will be used in the development of the final rules.

(7) *Requires use of current income.* In the past, schools could consider either the family's current rate of income or the family's income during the past 12 months to determine eligibility for free and reduced price meals.

Section 803 of Pub. L. 97-35 states that "any child who is a member of a household whose income, at the time the application is submitted, is at an annual rate which does not exceed the applicable family size income level" is eligible to receive free or reduced price meals. The Department proposes to define "current income" as income at the time of application, if representative, and annualized. Current income would be determined based on the income received during the month prior to application and multiplied by 12, if such income is representative, or income received during the past 12 months in the case of farmers, the self-employed, migrant workers, or others if the past 12 months are more representative.

**Recordkeeping**

In addition to the above mentioned changes, the Department proposes to require State agencies to maintain records demonstrating compliance with all of the requirements of this proposal, and proposes to monitor for compliance during the management evaluation process.

**Solicitation of Comments**

The Department exercised its authority in the following areas and solicits comments thereon: (1) The definitions of "adult", "household", "documentation", and "current income"; (2) Requiring that verification be applied without regard to race, sex, color, national origin, age or handicap; (3) allowing schools involved in the pilot study to deviate from routine application and verification procedures; (4) Including on the application a question regarding food stamp participation for purposes of simplifying the verification process later in the school year; (5) Requiring households to report changes in circumstances; and (6) Requiring School Food Authorities to notify households of the denial of benefits.

**List of Subjects in 7 CFR Part 245**

Food assistance programs, Grant programs—social programs, National School Lunch Program, School Breakfast Program, Special Milk Program, Reporting and recordkeeping requirements.

## PART 245—DETERMINING ELIGIBILITY FOR FREE AND REDUCED PRICE MEALS AND FREE MILK IN SCHOOLS

Accordingly, Part 245 is proposed to be amended as follows:

(1) In § 245.1 paragraph (a) is revised to read as follows:

**§ 245.1 General purpose and scope.**

(a) This part establishes the responsibilities of State agencies, Food and Nutrition Service Regional Offices (where applicable), and School Food Authorities in providing free and reduced price meals and free milk in the National School Lunch Program (7 CFR Part 210), the School Breakfast Program (7 CFR Part 220), the Special Milk Program for Children (7 CFR Part 215), and commodity schools. Section 9 of the National School Lunch Act, as amended, and Sections 3 and 4 of the Child Nutrition Act of 1966, as amended, require schools participating in any of the programs and commodity schools to make available, as applicable, free and reduced price lunches, breakfasts, and, at the option of the School Food Authority for schools participating only in the Special Milk Program, free milk to eligible children.

* * * * *

(2) In § 245.2 definition (a) "Commodity only school" is redesignated as (a-1). New definitions (a) "Adult", (a-2) "Current income", and (d-2) "Household" are added.

**§ 245.2 Definitions.**

(a) "Adult" means any individual 21 years of age or older.

* * * * *

(a-2) "Current income" means income, as defined in § 245.6(a), received during the month prior to application, if representative, and multiplied by 12, or for farmers, self-employed persons, migrant workers, or other income received during the past 12 months, if more representative.

* * * * *

(d-2) "Household" means "family" as defined in § 245.2(b).

* * * * *

(3) In § 245.2, definition (e) "Income poverty guidelines" is amended by removing the word "poverty" and inserting in its place the word "eligibility."

(4) In § 245.3, paragraph (a) the last sentence is revised to read as follows:

**§ 245.3 Eligibility standards and criteria.**

(a) * * * Such family size income standards for free and reduced price meals and for free milk shall be in accordance with Income Eligibility Guidelines published by the Department by notice in the **Federal Register.**

* * * * *

(5) In § 245.3, paragraph (c) the second sentence is removed.

(6) Section 245.3 is amended by removing paragraph (d) in its entirety. That paragraph contained instructions to implement Public Law 96-499 and the paragraph is now obsolete.

(7) In § 245.5(a)(1), paragraphs (i), (ii) and (vi) are revised to read as follows. The period ending paragraph (vii) is removed and replaced with a semi-colon. New paragraphs (viii) and (ix) are added.

**§ 245.5 Public announcement of the eligibility criteria.**

* * * * *

(a)(1) * * * (i) The Income Eligibility Guidelines for *reduced price* meals with an explanation that households with incomes less than or equal to the reduced price criteria would be eligible for free or reduced price meals (the Income Eligibility Guidelines for free meals shall *not* be included in letters or notices to such applicants unless the applicant is applying for benefits in the Special Milk Program); (ii) an explanation that the information on the application may be verified at any time during the school year; * * * (vi) the statement: "In the operation of child feeding programs, no child will be

discriminated against because of race, sex, color, national origin, age, or handicap"; * * * (viii) an explanation that recipients of free and reduced price benefits must notify the appropriate school officials of any changes during the school year in family size and increases in level of income which exceed $25 per month; and (ix) an explanation that a completed and signed application is a prerequisite to be considered for free and reduced price benefits.

* * * * *

(9) Section 245.6(a) is amended as follows:

(a) In § 245.6(a) the introductory paragraph is amended by adding the word "current" between the words "with respect to the" and "annual income of" in the third sentence and by revising the phrase at the end of the introductory paragraph as set forth below.

(b) Paragraph (a) is further amended by revising paragraph (a)(1) and the first two sentences of paragraph (a)(2) as set forth below, and by removing the phrase "for cause" from the third sentence of paragraph (a)(2).

**§ 245.6 Application for free and reduced price meals and free milk.**

(a) * * * The application shall require applicants to provide the social security number of all household members 21 years of age or older, an indication that application for one has been made or in the case of aliens ineligible for social security numbers, an indication that none can be acquired. The application shall contain substantially the following statements; (1) "In certain cases foster children are eligible for free or reduced price meals or free milk regardless of your family income. If you have such children living with you and wish to apply for such meals or milk for them, please contact us." and (2) "Section 9 of the National School Lunch Act requires that the social security number of each adult household member be given as a condition of eligiblity. The social security numbers may be used for verification of the information on the application. Failure to provide social security number information shall result in a denial of benefits." In addition the application must enable the applicant to indicate whether the household is participating in the Food Stamp Program. * * *

* * * * *

(10) In § 245.6, paragraph (b) is revised to read as follows and new paragraph (b-1) is added.

* * * * *

(b) *Determination of eligibility.* When a completed application furnished by a family indicates that the family meets the eligibility criteria for free or reduced price meals or free milk, the children from that family shall be provided the benefits to which they are entitled. School officials may seek verification of the information on the application. When the information furnished by the family is not complete or does not meet the eligibility criteria for free or reduced price benefits, school officials shall provide written notice to each family denied benefits. At a minimum, this notice shall include: (1) The reason for the denial of benefits, e.g. income in excess of allowable limits or incomplete application; (2) notification of the right to appeal; (3) instructions on how to appeal; and (4) a statement reminding parents that they may reapply for free and reduced price benefits at any time during the school year. The reasons for ineligibility shall be properly documented and retained on file at the School Food Authority, as appropriate.

(b-1) *Appeals of denied benefits.* A family who wishes to appeal a denied application by the School Food Authority shall do so under the hearing procedures established under § 245.7. However, prior to initiating the hearing procedure, the parent may request a conference to provide the opportunity for the parent and school officials to discuss the situation, present information, and obtain an explanation of the data submitted in the application or the decision rendered. The request for a conference shall not in any way prejudice or diminish the right to a fair hearing. The School Food Authority must promptly schedule a fair hearing, if requested.

* * * * *

(11) In § 245.6, an new paragraph (d) is added to read as follows:

**§ 245.6 Application for free and reduced price meals and free milk.**

* * * * *

(d) School Food Authorities which are involved in the Department's pilot study on income verification may be exempted from the requirements of this section and shall obtain verification and documentation as directed by the Department.

(12) In § 245.10, a new paragraph (f) is added to read as follows:

**§ 245.10 Action by School Food Authorities.**

* * * * *

(f) School Food Authorities verifying the information on the free and reduced price application shall ensure that verification activities are applied without regard to race, sex, color, national origin, age, or handicap.

(13) In § 245.11, a new paragraph (g) is added to read as follows:

**§ 245.11 Action by State agencies and FNSRO's**

* * * * *

(g) State agencies or FNSRO's, as applicable, verifying the information on the free and reduced price application shall ensure that verification activities are applied without regard to race, sex, color, national origin, age, or handicap.

(Sec. 803; Pub. L. 97-35; 95 Stat. 521-535; (42 USC 1758))

Signed in Washington, D.C. on May 21, 1982.

**John W. Bode,**

*Deputy Assistant Secretary for Food and Consumer Services.*

[FR Doc. 82-14366 Filed 5-24-82; 8:45 am]

BILLING CODE 3410-30-M

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## 7 CFR Part 245

## Determining Eligibility for Free and Reduced Price Meals and Free Milk in Schools; Verification of Eligibility

**AGENCY:** Food and Nutrition Service, USDA.

**ACTION:** Proposed rule.

**SUMMARY:** This rule proposes to amend Part 245 to implement several provisions of section 803 of Pub. L. 97-35, the Omnibus Budget Reconciliation Act of 1981. Under this proposal, minimum standards are established for the verification of the information on applications for free or reduced price meals or free milk benefits served in the National School Lunch, School Breakfast, Commodity School and Special Milk Programs. This proposal is intended to prevent errors and abuse in the delivery of free and reduced price benefits.

**DATES:** To be assured of consideration, comments must be postmarked on or before July 26, 1982. Since this proposal is one of two proposals regarding the provisions of section 803, commentors should clearly indicate that comments reference the proposed rule, "Verification of Eligibility."

**ADDRESSES:** Comments should be sent to Stanley C. Garnett, Branch Chief, Policy and Program Development Branch, School Programs Division, Food and Nutrition Service, USDA, Alexandria, Virginia 22302. All written submissions will be available for public inspection in Room 509, 3101 Park Center Drive, Alexandria, Virginia 22302, during regular business hours

(8:30 a.m. to 5:00 p.m.), Monday through Friday.

**FOR FURTHER INFORMATION CONTACT:** Mr. Garnett at the address listed above, or call (703) 756–3620.

**SUPPLEMENTARY INFORMATION:**

## Classification

This proposed action has been reviewed under Executive Order 12291 and has been classified *not major.* We do not anticipate that this proposal will have an impact on the economy of more than $100 million. The proposed rule is intended to ensure that free and reduced price benefits are directed to only those children from families whose income fall within the Income Eligibility Guidelines set forth by the Department by household size. No major increase in cost or prices for program participants; individual industries; Federal, State or local government agencies; or geographic regions is anticipated. This proposal is not expected to have significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or foreign markets.

This proposal has also been reviewed with regard to the requirements of Pub. L. 96–354, the Regulatory Flexibility Act. Samuel J. Cornelius, Administrator of the Food and Nutrition Service, has certified that this proposed rule does not have a significant economic impact on State agencies and local School Food Authorities.

In accordance with the Paperwork Reduction Act of 1980 (Pub. L. 96–511), the reporting and recordkeeping requirements contained in this proposed rule will be submitted to the Office of Management and Budget for approval. They are not effective until OMB approval has been obtained.

## Background

Prior to the passage of Pub. L. 97–35, section 9 of the National School Lunch Act (Act) provided that school officials "may for cause seek verification of the data in such application." The "for cause" provision limited verification to those situations where school officials had actual cause to believe the information furnished on the application was erroneous. For that reason, verification of the information on free and reduced price applications has been an infrequent occurrence.

Section 803 of Pub. L. 97–35 made several changes to the Act which affected the free and reduced price meal or free milk application process. While most of the changes affect the information collected on the application, several changes concern the verification of that information. Specifically, section 803 authorizes the Secretary, States, and local School Food Authorities to seek verification of the data contained in the application. Further, local School Food Authorities are *required* to undertake such verification procedures as may be prescribed by the Secretary, and to make appropriate changes in the eligibility determinations on the basis of such verification.

In response to the provisions of section 803 of Pub. L. 97–35, the Department is publishing two proposed rules.

This proposal, Verification of Eligibility, is designed to emplement the verification provisions of section 803 that do not have an immediate impact on the application process at the beginning of the school year. This proposal addresses the verification of information on free and reduced price applications, the notification to households when benefits are reduced or terminated and State agency recordkeeping requirements. A 60-day public comment period is provided to ensure that the public has sufficient opportunity for comment. Based on an analysis of the comments, the Department intends to publish an interim rule early next school year to allow schools and States to gain operational experience with verification procedures. Comments will be solicited on that interim rule and will be considered in the development of a final rule.

Another proposed rule, Revised Application Procedures (published in today's **Federal Register**), is designed to implement those provisions of section 803 affecting the application process at the beginning of the school year. Many of those provisions are nondiscretionary. Normally, the Department would publish nondiscretionary provisions as a final rule since public comment is unnecessary. However, the Revised Application Procedures rule contains several ancillary provisions which are subject to Departmental discretion. For this reason, the Department intends to provide a 30-day public comment period for that rule. That abbreviated comment period will provide time for the Department to analyze the comments and publish an interim rule in sufficient time to affect the 1982–83 application process.

Based on an analysis of comments received for both interim regulatory actions, the Department expects to publish one final rule which would implement both the discretionary and nondiscretionary provisions. A Spring, 1983 publication date is anticipated.

## Proposed Verification

In developing this proposal the Department has sought to strike a balance between two competing concerns. First, there are abuses in the current free and reduced price application system, as documented in audits and reviews, which must be addressed through a viable income verification system. Second, States and local school officials do not have unlimited resources available to perform verification. The Department believes this draft rule will provide for a viable system without over burdening States and local officials. Moreover, States which find even the minimum requirements too onerous may request a waiver so long as they can demonstrate that an alternate system can achieve the same results.

Section 803 of Pub. L. 97–35 allows the Secretary, State agencies, and local School Food Authorities to seek verification of the information provided on applications for free and reduced price meals and free milk. The Act also requires local School Food Authorities to comply with the regulations prescribed by the Secretary concerning verification of information.

The Department believes that the possibility of verification should greatly deter under-reporting of household income of falsification of household composition. Such verification should also result in increased reporting of changes of household circumstances during the school year. For these reasons, the Department proposes to require verification of some free and reduced price applications.

Under this proposal, State agencies are required to ensure that for School Year 1982–83, at a minimum, three (3) percent or 3,000 (whichever is less) of all applications on file in each School Food Authority by October 15 are verified. State agencies have the option of using State agency staff or requiring local School Food Authorities to meet this requirement. State agencies delegating the verification responsibility to local School Food Authorities must ensure that the School Food Authorities satisfy this minimum verification requirement by January 1 of the school year. State agencies may request a waiver from FNS in regard to these verification requirements. FNS may approve the waiver if the State is able to demonstrate an alternative approach that will achieve the same results. In either case, verification may occur prior to the approval of applications;

however, the pursuit of verification shall not unduly delay the issuance of benefits to eligible children.

States which decide to meet the requirements at the State level may want to consider meeting the requirement during an AIMS review or audit or during an A-102 audit. The State may want to consider using the social security number provided on the application form to verify wages earned or other benefits through computer matching of the income reported. Should the State delegate the responsibility to the School Food Authority level, a variety of approaches become feasible. These approaches include the collection of written verification such as wage stubs, collateral contacts, and cross-program exchange of information. The Department views the verification requirement as a minimum with sufficient flexibility to allow States and local School Food Authorities to implement the requirements within existing frameworks without extensive additional financial burden.

The Department expects that most schools will opt to collect written verification of income directly from the household. This option is the most universally applicable, places the burden of responsibility on the household, and creates an awareness in the community that verification of eligibility does occur. The parent should receive clearly worded notification that the household has been selected for review and must submit the requested verification to maintain eligibility for free or reduced price benefits. The notice to parents should clearly describe the types of verification acceptable to the school, e.g. wage stubs, award letters from social security, benefit statements for unemployment compensation, court orders specifying alimony or child support, etc. Further, the notice should give the name and telephone number of the school official who can answer questions and assist the household in acquiring the necessary verification.

The initiation of collateral contacts can be used in those situations where the household is unable to acquire documentary verification. Collateral contacts can be made in person, over the phone, or by mail. The results of the contact should be written on or attached to the application noting the date, person contacted, results, and the name of the school official making the contact.

Cross-program exchange of information is another method of verification that may be utilized. State agencies and School Food Authorities should contact legal counsel to ensure that cross-program exchanges do not violate any State or Federal laws.

The Department believes an abbreviated verification procedure will suffice for food stamp households. These households undergo extensive verification in order to receive food stamp benefits. A State agency or School Food Authority may require the applicant to demonstrate current eligibility for food stamp benefits by providing "notice of eligibility" or other evidence of benefits.

An abbreviated verification procedure for food stamp households should minimize the administrative burden and cost of verification efforts since most free meal recipients are also eligible for food stamp benefits.

State agencies or local School Food Authorities would be required, under this proposal, to apply the verification efforts uniformly without regard to race, sex, color, national origin, age, or handicap. Since State and local laws differ widely, each State agency and School Food Authority should contact its legal counsel to ensure compliance with applicable laws.

**Proposed Notification Requirements**

The State agency or School Food Authority must terminate or reduce household benefits, if (a) the household refuses to cooperate with verification efforts, or (b) the verification effort indicates the household is ineligible to receive benefits or is eligible to receive fewer benefits. The School Food Authority must immediately notify the household in writing of a reduction or termination of benefits and allow 10 days before such termination or reduction takes place. The notice must advise the household of the change, the reasons for the change, the right to appeal the action within 10 day advance notice period and provide instructions on how to appeal. The reasons for ineligibility or reduction of benefits must be properly documented and retained on file at the School Food Authority.

**Proposed Continuation of Benefits**

Households which have been approved for benefits and which are subject to a reduction or termination of benefits later in the *same* school year will continue to receive benefits subject to the hearing official's decision if they appeal the adverse action within the 10 day advance notice period. Households which are denied benefits upon application shall not receive benefits pending an appeal of the decision.

**Proposed Recordkeeping**

State agencies will be required to maintain records demonstrating compliance with these minimum documentation and verification requirements. The Department will monitor for compliance during the management evaluation process.

**List of Subjects in 7 CFR Part 245**

Food Assistance Programs, Grant programs—Social programs, National School Lunch Program, School Breakfast Program, Special Milk Program, Reporting and recordkeeping requirements.

## PART 245—DETERMINING ELIGIBILITY FOR FREE AND REDUCED PRICE MEALS AND FREE MILK IN SCHOOLS

Accordingly, Part 245 is proposed to be amended as follows:

1. In § 245.2, new paragraph (k) is added as follows:

**§ 245.2 Definitions.**

* * * * *

(k) "Verification" means substantiation of the information provided on the free or reduced price application. Verification may include but is not limited to the use of wage stubs, award letters, letters from employers, third party contacts, and computerized wage/income matching.

2. New § 245.6a is added as follows:

**§ 245.6a Verification requirements.**

(a) *Verification requirements.* State agencies and FNSROs, as applicable, shall ensure that for School Year 1982-83, three (3) percent or 3,000 (whichever is less) of all applications on file in each School Food Authority by October 15 are verified over the course of the school year. State agencies may request a waiver from FNS in regard to the verification requirements; *Provided,* that an alternative approach to achieve the same results is submitted in writing to and approved by FNSRO. The State agency or FNSRO, as applicable, may verify the information on the application or it may delegate the responsibility to all or selected School Food Authorities. State agencies delegating the verification responsibility to local School Food Authorities shall ensure that the School Food Authorities satisfy this minimum verification requirement by January 1 of the school year. Verification for recipients of food stamp benefits may be limited to a review to determine that the period of eligibility for food stamp benefits is current. If the food stamp certification period is found to have expired, the household shall be subject to routine verification of eligibility. Verification may occur prior to the approval of applications;

however, the pursuit of verification shall not unduly delay the issuance of benefits to eligible children. The Department encourages State agencies to verify during the first part of the school year. School officials shall, at a minimum, undertake the verification requirements prescribed by the State agency. If an applicant refuses to cooperate with the efforts to verify, eligibility shall be terminated in accordance with § 245.6a(d).

(b) *Recordkeeping.* State agencies and FNSROs, as applicable, shall maintain on file for review, a description of the verification to be accomplished during each school year. The description shall include: (1) A summary of the verification efforts including the techniques to be used; (2) the locations where verification will take place; (3) the entity responsible for verification (e.g., State agency, School Food Authority); (4) the total number of applications on file in the State by October 15 of each school year; and (5) the percentage or number of applications to be verified in the State for the current school year.

(c) *Nondiscrimination.* The verification efforts shall be applied without regard to race, sex, color, national origin, age, or handicap.

(d) *Notification.* School officials shall immediately notify families of the denial of benefits as specified in § 245.6(b). Advance notification shall be provided to families which receive a reduction or termination of benefits 10 calendar days prior to the actual reduction or termination. The notice shall advise the household of: (1) The change; (2) the reasons for the change; (3) notification of the right to appeal the action within the 10 day advance notice period; and (4) instructions on how to appeal. The reasons for ineligibility shall be properly documented and retained on file at the School Food Authority.

3. In § 245.7, paragraph (a)(ix) is amended to add the words "and that the decision of the hearing official is binding" after the word "official" and before the semi-colon.

4. In § 245.7, new paragraph (b) is added as follows:

**§ 245.7 Hearing procedures for families and School Food Authorities.**

* * * * *

(b) *Continuation of benefits.* When a household disagrees with an adverse action which affects its benefits and requests a fair hearing; benefits shall be continued as follows while the household awaits the hearing:

(1) Households which have been approved for benefits and which are subject to a reduction or termination of benefits later in the *same* school year, shall receive continued benefits if they appeal the adverse action within the 10 day advance notice period; and

(2) Household which are denied upon application shall not receive continued benefits.

(Sec. 803, Pub. L. 97-35, 95 Stat. 521-535 (42 U.S.C. 1758))

Signed on May 21, 1982.

**John W. Bode,**

*Deputy Assistant Secretary for Food and Consumer Services.*

[FR Doc. 82-14366 Filed 5-24-82; 8:45 am]

BILLING CODE 3410-30-M

5-25-82
Vol. 47—No. 101
Book 2:
Pages:
22711-22930

# federal register

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Tuesday, May 25, 1982

## Part V

# Department of Health and Human Services

### Food and Drug Administration

### Over-the-Counter Oral Health Care and Discomfort Drugs; Establishment of a Monograph

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 354**

**[Docket No. 80N-0228]**

## Drug Products for the Relief of Oral Discomfort for Over-the-Counter Human Use; Establishment of a Monograph

**AGENCY:** Food and Drug Administration.

**ACTION:** Advance notice of proposed rulemaking.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which over-the-counter (OTC) drug products for the relief of oral discomfort (drugs which relieve oral discomfort when applied topically to teeth and gums) are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review panel on OTC Dentifrice and Dental Care Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

**DATES:** Written comments by August 23, 1982 and reply comments by September 22, 1982.

**ADDRESS:** Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

**SUPPLEMENTARY INFORMATION:** In accordance with Part 330 (21 CFR Part 330), FDA received on July 13, 1978 a report on OTC drug products for the relief of oral discomfort from the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products. This report is one of three issued by this Panel. Other reports by this Panel concerned oral mucosal injury drug products (published in the **Federal Register** of November 2, 1979 (44 FR 63270)) and anticaries drug products (published in the **Federal Register** of March 28, 1980 (45 FR 20666)). FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC drug products for the relief of oral discomfort are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC drug products for the relief of oral discomfort as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC drug products for the relief of oral discomfort will be stated initially when the tentative final monograph is published in the **Federal Register** as a proposed regulation. In the preamble to the tentative final monograph, the agency also will announce its initial determination whether the monograph is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the tentative final monograph is published. At that time FDA also will consider whether the monograph has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC drug products for the relief of oral discomfort. Types of impact, may include, but are not limited to, the following: increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC drug products for the relief of oral discomfort should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC drug products for the relief of oral discomfort submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after June 24, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III durgs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, on OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in dentifrice and dental care drug products, except mouthwashes and oral antiseptics, was issued in the **Federal Register** of January 30, 1973 (38 FR 2781). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ")

Under § 33.10(a) (1) and (5), the Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of those products:

Louis P. Gangarosa, D.D.S., Ph. D., Chairman
Joseph J. Aleo, D.D.S., Ph. D. (appointed September 1, 1973)
Howard H. Chauncey, D.M.D., Ph. D. (resigned April 30, 1976)
Valerie Hurst, Ph. D.
Joy B. Plein, Ph. D.
Delos E. Raymond, D.D.S.
Roger H. Scholle, D.D.S., M.S.
Lawrence E. VanKirk, Jr., D.D.S., M.P.H. (appointed June 29, 1976)
Benjamin O. Watkins D.D.S. (resigned August 1, 1973)

Nonvoting liaison members served on the Panel as follows: Judy Jackson, Esq., nominated by the Consumer Federation of America, served as the consumer liaison until April 1974 followed by Mary Plaska, nominated by the American Public Health Association, until May 1976 followed by Sandra Zimmerman, nominated by the Consumer Federation of America. Lester D. Apperson, Ph. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, served as an industry liaison. Joseph L. Kanig, Ph. D., nominated by the Proprietary Assocation, also served as an industry liaison until January 1978.

The following FDA employee assisted the Panel: Clarence C. Gilkes, D.D.S., served as Executive Secretary. Michael D. Kennedy served as Panel Administrator until January 1978 followed by Thomas D. DeCillis, R. Ph. Melvin Lessing, M.S., R. Ph. served as Drug Information Analyst until June 1977. George Kerner, M.S., served as Consumer Safety Officer. Cindy Barkdull served as special assistant from July 1977 to April 1978. Elmer M. Plein, Ph. D., and Gordon H. Schrotenboer, Ph. D., served as consultants to the Panel.

The Panel was first convened on April 24, 1973, in an organizational meeting. Working meetings were held on May 24 and 25, June 21 and 22, August 15 and 16, October 10 and 11, November 29 and 30, 1973; January 17 and 18, February 27 and 28, April 3 and 4, May 9 and 10, June 19 and 20, July 24 and 25, September 19 and 20, October 16 and 17, December 4 and 5, 1974; January 15 and 16, February 26 and 27, April 2 and 3, May 7 and 8, June 24 and 25, August 12, 13, and 14, October 9 and 10, December 3 and 4, 1975; January 23 and 24, February 24 and 25, March 31 and April 1, May 11 and 12, June 30 and July 1, July 28 and 29, August 25, and 26, October 5 and 6, December 1 and 2, 1976; January 12 and 13, March 9 and 10, April 20 and 21, June 1 and 2, July 13 and 14, August 24 and 25, October 19 and 20, November 30 and December 1, 1977. January 17 and 18, March 11 and 12, April 26, 27, and 28, May 30 and 31, and June 1, and July 11, 12, and 13, 1978.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above).

The following individuals were given on opportunity to appear before the Panel to express their views either at their own or at the Panels' request on all issues before the Panel:

John E Alman, M.A.
Hazen J. Baron, D.D.S., Ph. D.
I. B. Bender, D.D.S.
Robert Blank, Ph. D.
Malcolm Boone, D.D.S.
R. K. Boutwell, Ph. D.
Herbert Brilliant, D.D.S.
Richard C. Brogle, Ph. D.
Finn Brudevold, D.D.S.
Lewis P. Cancro, Ph. D.
A. Chasens, D.D.S.
Neal W. Chilton, D.D.S.
Stephen A . Cooper , D.M.D., Ph. D.
D. Walter Cohen, D.D.S.
William E. Cooley, Ph.D.
Robert Ellison, D.D.S., M.S.
H. Fogels, D.D.S.
Sol Gershon, Ph. D.
William Gold, Ph. D.
Hary Gordon, Ph. D.
Hans Graf, D.D.S.
F. Healy, Ph. D.
John Hefferren, Ph. D.
L. Kenneth Hiller, Ph. D.
George F. Hoffnagle, Sc. D.
Herschel S. Horowitz, D.D.S., M.P.H.
Homer Jamison, D.D.S., Ph. D.
Marvin Kamisky, Ph. D.
Krishan Kapur, D.M.D., M. Sc.
Kenneth Kasses, Ph. D.
Phillip B. Lawson
Edgar Lazo-Wasem, Ph. D.
Donald A. M. MacKay, Ph. D.
John H. Manhold D.M.D.
Craig R. Means, D.D.S., M. Sc.
Murray Rosenthal, M.S.
Albert L. Russell, D.D.S., M. Ph.
Bernard Schneider, D.D.S.
James H. Stanton
Willard J. Tarbet, D.D.S., Ph. D.
Patrick Toto, D.D.S.
Leonard Townes, D.D.S.
Aaron Trubman, D.D.S.
Paul Vinton, D.D.S.
Carrol S. Weil, M.A.
Elizabeth K. Weisburger, Ph. D.
S. C. Yankell, D.D.S.
K. Yeh, Ph. D.
A. Albert Yurkstas, D.M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel was charged to review submitted data and information for OTC dentifrice and dental care drug products.

Because all such agents are not used for the same purpose, it was not possible for the Panel to establish a single standard of requirements for effectiveness of each product. Therefore, in an attempt to simplify categorization of ingredients and labeling claims, the Panel placed the dental care drug products into the following therapeutic classifications: (1) Agents for oral mucosal injury, (2) agents for the relief of oral discomfort, (3) anticaries agents, (4) dental plaque disclosing agents, and (5) denture aids.

On May 28, 1976, the Medical Device Amendments of 1976 became law. This legislation amends the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) and provides new authority to assure the safety and effectiveness of medical devices. Several products previously regulated as drugs that were under review by the Panel came within the definition of a medical device under these amendments. The FDA reviewed the products previously regarded as drugs and concluded that the following products as published in the **Federal Register** of December 16, 1977 (42 FR 63472) fall within the definition of a medical device: denture cushions, dental adhesives, dental reliners and repair kits, denture cleansers, and plaque-disclosing kits. The Panel wishes to point out that during its deliberations "kits" were not specifically addressed and that the Panel's terminology for dental devices differs from that published in the **Federal Register**. The Panel used the following terminology in evaluating these products: denture adhesives, denture reliners, denture repair products, denture cleansers, and dental plaque-disclosing agents.

In a notice published in the **Federal Register** of May 2, 1978 (43 FR 18769), FDA announced that it had transferred the responsibility for regulating OTC dental care devices from the agency's Bureau of Drugs to its Bureau of Medical Devices (BMD). In addition, the notice announced that the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products had summarized its findings and recommended that the agency transfer that portion of its report concerning products now regulated as medical devices, together with the data and information submitted in response to the January 30, 1973 notice, to BMD. A summary of the Panel's conclusions concerning the safety, effectiveness, and labeling of those products is included in the Panel's minutes for the March 11 and 12, 1978 meeting.

The Panel presents its conclusions and recommendations for drug products for the relief of oral discomfort in this document. The Panel's conclusions and recommendations for oral mucosal injury drug products were published in the **Federal Register** of November 2, 1979 (44 FR 63270) and the Panel's conclusions and recommendations for anticaries drug products were published in the **Federal Register** of March 28, 1980 (45 FR 20666).

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through July 13, 1978, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC drug products for the relief of oral discomfort are set out in three categories:

*Category I.* Conditions under which OTC drug products for the relief of oral discomfort are generally recognized as safe and effective and are not misbranded.

*Category II.* Conditions under which OTC drug products for the relief of oral discomfort are not generally recognized as safe and effective or are misbranded.

*Category III.* Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 25 ingredients for relief of oral discomfort. The Panel placed one ingredient in Category I, three ingredients in Category II, and nine ingredients in Category III for use as agents for the relief of toothache. The Panel placed three ingredients in Category I, two ingredients in Category II, and three ingredients in Category III for use as oral mucosal analgesics. The Panel placed one ingredient in Category I, no ingredients in Category II, and one ingredient in Category III for use as oral mucosal protectants. The Panel placed no ingredients in Category I, one ingredient in Category II, and five ingredients in Category III for use as tooth desensitizers. (The number of ingredient classifications does not equal the number of ingredients reviewed because some ingredients were reviewed for more than one labeled use.)

## I. Submission of Data and Information

Pursuant to the notice published in the **Federal Register** of January 30, 1973 (38 FR 2781) requesting the submission of data and information on OTC dentifrice and dental care drug products, the following firms made submissions relating to the indicated products that, the Panel has further determined, contain active ingredients or labeling which may be appropriately classified as drug products for the relief of oral discomfort.

### *A. Submissions by Firms*

**Firms and Marketed Products**

Abbott Laboratories, North Chicago, IL 60064, Butyn Metaphen Dental Ointment.

A-Trol Laboratories, Topeka, KA 66604, I.D. Denture Medication.

Block Drug Co., Jersey City, NJ 07302, Jiffy Toothache Drops, Poloris Poultices, Sensodyne.

Commerce Drug Co., Inc. Farmingdale, NY 11735, Ora-Jel, Baby Ora-Jel, Ora-Jel D.

C. S. Dent & Co., Cincinnati, OH 45202, Dent's Toothache Drops, Dent's Toothache Gum, Dent's Lotion-jel, Dent's Dental Poultice.

Denver Chemical Manufacturing Co.; Stamford, CT 06904, Dr. Hand's Teething Gel, Dr. Hand's Teething Lotion, Pain-A-Lay.

Eaton Laboratories, Norwich, NY 13815. Chloraseptic Mouthwash and Gargle.

Eneglotaria Medicine Co., Inc., Santurce, PR 00907, Gotas Dentil, Erpen.

John Arthur Geyer Co., Bedford, NH 03102, Kank-A.

International Pharmaceutical Corp., Warrington, PA 18976, DeSense Dental Gel, Protect Dental Gel.

K. I. K. Co., Bethlehem, PA 18016, Cheramist #30.

Lorvic Corp., Saint Louis, MO 63134, Desensitizer.

McKesson Laboratories, Fairfield, CT 06430, OraFix Medicated.

Pfizer, Inc., New York, NY 10017, Thermodent Toothpaste.

Red Cross Chemical Works, Inc., Chicago, IL 60647, Toothache Outfit.

Rilox Co., Inc., New Orleans, LA 70122, Creole Toothache Wax.

Rystan Co., Inc., White Plains, NY 10605, Chloresium Toothpaste, Chloresium Dental Ointment, Chloresium Solution.

Sanlor Laboratories, Washington, DC 20006, Endoflas, F.S.

Vick Chemical Co., New York, NY 10017, Benzodent Analgesic Denture Ointment.

Whitehall Laboratories, Inc., New York, NY 10017, Anbesol.

Zelite Corp., New York, NY 10017, Dent-Zelite Toothache Remedy.

In addition, the following firms made related submissions:

Abbott Laboratories, North Chicago, IL 60064, Butyn Metaphen Dental Ointment (Additional data).

Block Drug Co., Jersey City, NJ 07302, Sensodyne, Poloris Dental Poultice (Additional data).

Commerce Drug Co., Inc., Farmingdale, NY 11735, Baby Ora-Jel (Additional data).

Eaton Laboratories, Norwich, NY 13815, Chloraseptic Mouthwash and Gargle (Additional data).

International Pharmaceutical Corp., Warrington, PA 18976, Protect Dental Gel (Additional data).

Rystan Co., Inc., White Plains, NY 10605, Chloresium Toothpaste, Chloresium Dental Ointment, Chloresium Solution (Additional data).

Sanlor Laboratories, Washington, DC 20006, Endoflas, F.S. (Additional data).
Vick Chemical Co., New York, NY 10017, Vicks Potassium Nitrate Toothpaste, Testing Method.
Whitehall Laboratories, Inc., New York, NY 10017, Anbesol (Additional data).

*B. Ingredients Submitted to the Panel*

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Alcohol
Beeswax
Benzocaine
Benzoin compound tincture
Benzyl alcohol
Boric acid
Butacaine
Calcium carbonate
Camphor
Capsicum oleoresin (capsicum)
Carbolic acid (phenol)
Cellulose gum
Chloroform
Citric acid
Clove oil
Creosote
Cresol
D & C Red Color 11251
Distilled water
Edetate disodium (EDTA)
Eugenol
Fluidextract myrrh
Formaldehyde
Glycerin
Hamamelis water
Hops
Hydroxyquinoline sulfate
Iodine
Magnesium aluminum silicate
Menthol
Methylparaben
Methyl salicylate
Nitrogen, compressed (propellant)
Nitromersol chloride
Oil of cassia
Oil of cloves
Oxyquinoline
Paraffin wax (paraffine)
Pellitory tincture
Petrolatum
Phenol
Pluronic F-127™ gel
Potassium nitrate
Potassium sulfate
Propylene glycol
Propylparaben
Sandarac
Sassafras root
Silica
Sodium bicarbonate
Sodium borate
Sodium chloride
Sodium citrate
Sodium fluoride
Sodium lauryl sulfate
Soduim phenolate
Sodium saccharin
Sodium sulfate
Sorbitol
Stannous fluoride
Strontium chloride
Thymol
Thymol iodide
Water

2. *Other ingredient reviewed by the Panel in addition to the submitted data.*

Sodium monofluorophosphate

*C. Classification of Ingredients*

1. *Active ingredients.*

Benzocaine
Benzoin preparations (benzoin tincture and compound benzoin tincture)
Benzyl alcohol
Butacaine sulfate (butacaine)
Camphor
Capsicum (capsicum oleoresin)
Citric acid
Clove oil (oil of cloves)
Creosote
Cresol
Eugenol
Formaldehyde solution (formaldehyde)
Menthol
Methyl salicylate
Myrrh, fluidextract (fluidextract myrrh)
Phenol (carbolic acid)
Phenolate sodium (sodium phenolate)
Potassium nitrate
Sodium citrate
Sodium fluoride
Sodium monofluorophosphate
Stannous fluoride
Strontium chloride
Thymol
Thymol iodide

2. *Inactive ingredients.*

Beeswax
Calcium carbonate
Cellulose gum
Chloroform
Cinnamon oil (cassia oil, oil of cassia)
D & C red color 11251
Distilled water
Edetate disodium (EDTA)
Glycerin
Hops
Magnesium aluminum silicate
Nitrogen, compressed (propellant)
Paraffin wax (paraffine)
Petrolatum
Poloxamer 407 (Pluronic F-127™ gel)
Potassium sulfate
Propylene glycol
Propylparaben
Sandarac
Sassafras root
Silica
Sodium Bicarbonate
Sodium chloride
Sodium lauryl sulfate
Sodium saccharin
Sodium sulfate
Sorbitol
Water

3. *Ingredients deferred to the Advisory Review Panel on OTC Oral Cavity Drug Products.*

Alcohol (antiseptic)
Alum (astringent)
Boric acid (astringent)
Camphor (antimicrobial)
Iodine (antiseptic)
Hamamelis water (astringent)
Hydroxyquinoline sulfate (antiseptic)
Menthol (antiseptic)
Methylparaben (preservative)
Methyl salicylate (antiseptic)
Nitromersol chloride (antiseptic)
Oxyquinoline (antiseptic)
Pellitory tincture (astringent)
Phenol (antiseptic)
Propylparaben (antiseptic)
Sodium borate (antiseptic)

4. *Ingredients deferred to the Advisory Review Panel on OTC Miscellaneous External Drug Products.*

Camphor (cold sore claim)
Benzoin preparations (benzoin tincture and compound benzoin tincture) (Herpes simplex claims).

5. *Ingredients deferred to the Bureau of Medical Devices.*

Paraffin wax (paraffine) (as a denture cushion)

6. *Indications deferred to the Advisory Review Panel on OTC Oral Cavity Drug Products.*

All antiseptic claims:
"For rapid and effective relief of minor sore throat."
"For fast temporary relief of minor throat and mouth soreness."
"For rapid relief of minor throat and mouth soreness."

7. *Indications deferred to the Advisory Review Panel on OTC Miscellaneous External Drug Products.*

All cold sore and fever blister (Herpes simplex) claims.

*D. Referenced OTC Volumes*

The "OTC Volumes" cited throughout this document include submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of April 26, 1973 (38 FR 10306). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after June 24, 1982, in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62 5600 Fishers Lane, Rockville, MD 20857.

## II. General Statements and Recommendations

*A. Definitions*

The following definitions have been adopted by the Panel. These definitions reflect the Panel's intended meaning of terms as specifically used in this document in reference to drug products for the relief of oral discomfort. Some of these definitions also apply to the other drug categories reviewed by the Panel. Some degree of variation with other definitions of the same terms may exist.

1. *Agent for the relief of oral discomfort.* An agent which, when applied topically, has direct or indirect capability to relieve oral discomfort. This category of drugs includes oral mucosal analgesics, tooth desensitizers, oral mucosal protectants, and agents for the relief of toothache.

2. *Agent for the relief of toothache.* An ingredient used for the temporary relief of pain arising as a result of an open tooth cavity.

3. *Anesthetic.* A drug which causes reversible loss of feeling or sensation. Anesthetics are of two types. A "general" anesthetic is given by inhalation or by intravenous injection, and the agent causes loss of consciousness as well as loss of sensation. A "local" anesthetic is applied to the nerve tissue, in which it blocks sensory receptors and passage of nerve impulses. In a professional practice, the dentist administers local anesthetics by (1) injection into the area adjacent to the nerve(s) to be blocked, or (2) application of the agent (a "topical" or "surface anesthetic) to the oral mucosa. The term "oral mucosal analgesic" is used synonymously with "topical" or "surface anesthetic" or "topical analgesic."

4. *Analgesic (topical).* An ingredient used in drug products for surface application to provide temporary relief of discomfort by an anesthetic or analgesic effect.

5. *Anodyne.* "Anodyne" is synonymous with "topical analgesic." (See part II. paragraph A.4. above—Analgesic (topical).)

6. *Antiseptic.* A preparation which contains chemicals intended to kill or temporarily prevent multiplication of harmful germs which may be present on the skin or oral mucous membranes.

7. *Bioavailability.* The degree to which the drug is absorbed from a dosage form into the body or to its site of action.

8. *Buffering agent.* An agent or system which has the ability to resist a change in pH (hydrogen ion concentration), particularly in aqueous solution, upon the addition of an acid, alkali, or upon dilution with a solvent.

9. *Carcinogenic.* Producing cancer. Carcinogenic agents may be broadly categorized as (a) chemical, (b) physical, (c) viral, or (d) hormonal. Not all species are susceptible to every known carcinogen; it is common to find that a carcinogen which is active in one species will be inactive in another.

10. *Cementum.* The bonelike material covering the root of the tooth. Cementum contains about 45 to 50 percent organic and the balance, inorganic matter. It contains a great number of fibers which attach the tooth to the bone.

11. *Counterirritant.* An irritating drug that is applied locally to the skin or oral mucosa for relief of pain originating from a structure other than the site of application. For example, an irritant drug might be applied in a dental poultice to the oral mucosa surrounding a tooth with a painful pulpitis.

12. *Demulcent.* A protective agent which is employed primarily to alleviate irritation, particularly of mucous membranes or abraded tissues. It is also often applied to the skin.

13. *Dental calculus.* Mineralized dental plaque accumulates on the tooth surface principally at the gingival margin. One of the major fates of plaque is mineralization. Plaque serves as a matrix for calculus formation. The surface of calculus is usually covered with a nonmineralized layer of plaque. The main irritating feature of calculus is its surface plaque rather than its calcified surface or interior.

14. *Dental care agent.* Any drug or dosage form used to treat or prevent disease of the teeth or soft tissue in the oral cavity.

15. *Dental (dentin) hypersensitivity.* A term which implies that the teeth are much more reactive than normal to sensory stimuli such as heat, cold, sour, sweet, or touch. Hypersensitivity can occur when dentin is exposed to the oral environment as a result of gingival recession, abrasion, erosion, or a defect in the enamel or cementum.

16. *Dental poultice.* A topical dosage form which is confined within a porous sac and is applied to the oral mucous membrane in order to supply medication in the presence of heat and moisture.

17. *Dental rinse.* A term used to designate a liquid dosage form for rinsing between and around the teeth.

18. *Dentifrice.* In this document a dentifrice is a substance used with a toothbrush to clean the accessible surfaces of the teeth. Dentifrices are ordinarily composed of water, detergent, humectant, binder, flavoring agents, and a finely powdered abrasive as the principal ingredient. In this document a dentifrice is considered to be an abrasive-containing dosage form for delivering therapeutic agents to the teeth.

19. *Dentin.* Dentin is the calcified tissue forming the bulk of a tooth. It is composed of approximately 70 percent inorganic material, 18 percent organic material, and 12 percent water. Dentin is covered by the enamel of the tooth crown and the cementum of the root. It encloses the soft pulpal tissues of the tooth. Dentin has a tubular structure, and processes from cells in the pulp (odontoblasts) penetrate the dentinal tubules. There are three types of dentin—primary dentin, secondary dentin, and tertiary dentin.

a. *Dentin, primary.* The primary dentin is the well-structured dentin that is deposited during the original formation of a tooth. Dentin deposited later in life differs in structure and can be distinguished from primary dentin microscopically by a demarcation line that stains darkly.

b. *Dentin, secondary (reparative, irritation, adventitious, or tertiary dentin).* Dentin formed after the original primary dentin of the tooth has been deposited is termed "secondary dentin." It forms on the inner, or pulpal, surface of the primary dentin as a physiologic process or as a pathologic response to thermal, mechanical, or chemical irritants. The secondary dentin is not as well-structured as primary dentin and can be distinguished microscopically by its irregular morphologic pattern.

c. *Dentin, tertiary.* Although all dentin that is not primary dentin has traditionally been considered to be secondary dentin, some dental scientists now distinguish between secondary and tertiary dentin. The term "tertiary dentin" is used to designate dentin forming as the result of more severe injuries or insults to a tooth, such as dental caries, marked abrasion, or extensive erosion. The tertiary dentin is of very poor tubular structure and is limited to the area of irritation. In this context, secondary dentin differs from tertiary dentin in that secondary dentin forms as the result of mild biologic effects and is of a more generalized deposition.

In this document, evaluation of the active ingredients is not related to any specific type of dentin.

20. *Dentin desensitizer.* A drug which acts on the dentin to block perception of those stimuli which are usually not perceived by normal subjects but which are perceived by patients with dental hypersensitivity.

21. *Dentinal tubule.* Microscopic channels in the dentin which contain (a) the odontoblastic process (projection of the dentin-producing cells which line the pulp chamber and produce dentin), (b) tissue fluid bathing the process, and (c) varying degrees of mineral. It is controversial whether these tubules contain nerves, but there is general agreement that the tubules contain the means for transmitting pain perception.

22. *Dosage.* A schedule that includes the amount of drug that is ingested or applied at one time (the dose) and the time intervals at which the dose is given;

the schedule may include the duration of therapy.

23. *Dosage form.* The pharmaceutical preparation, e.g., solution, suspension, paste, tablet, ointment, in which the drug is administered.

24. *Dose.* The quantity of a drug that is ingested or applied at one time.

25. *Dose-response.* The relationship between the dose of a drug and the magnitude of the effect produced by that dose.

26. *Double-blind study.* A testing procedure in which neither the investigator nor the subject (patient) knows whether an experimental drug or its control has been administered.

27. *Enamel.* The compact and hard substance that covers the crown of the tooth and provides protection for the dentin. The inorganic content of mature enamel amounts to 96 to 97 percent, by weight, the remainder consisting of organic matter and water.

28. *Fluoride.* The term "fluoride" is used to denote the inorganic forms in which fluorine has combined with other elements. The term "fluoride ion" denotes the negatively charged atom of the chemical element fluorine. The deposition of fluoride in dental enamel has been shown to increase resistance to enamel solubility and, therefore, dental decay.

29. *Gingivitis.* Inflammation occurring in the marginal or papillary gingiva as a response to bacterial plaque.

30. *Hypersensitivity.* Literally means, "more sensitive than normal." In general health care, the term is almost synonymous with allergy and implies that the person has been exposed to a drug, develops antibodies to it, and then reacts adversely to the drug upon subsequent exposure, whereas the normal subject does not. (See part II. paragraph A.15 above—Dental (dentin) hypersensitivity.)

31. *Immediate dentures.* A denture is a dental prosthesis made to replace lost natural teeth in a dental arch. A partial denture replaces a few teeth; a full denture replaces all the lost teeth in an arch (upper or lower). An immediate denture is one that is fabricated prior to the extraction of a few natural teeth and placed in the mouth immediately following the extraction of the natural teeth as part of the surgical procedure.

32. *Minor gum disorders (injury).* Inflammation related to mechanical irritation or minor injury of the gingival tissues. The Panel does not consider gingivitis caused by dental plaque to be a minor gum disorder amenable to self-diagnosis or treatment by OTC preparations.

33. *Mouthwash (oral rinse).* A solution often containing breath-sweetening, astringent, demulcent, detergent, or germicidal agents which is used for freshening and cleansing the mouth, or for gargling. In some instances, such a vehicle may be used to deliver an active drug to the oral mucosa or teeth. The Panel prefers the terms "oral rinse" and "dental rinse" according to their respective areas of use (for the oral mucosa or the teeth) rather than "mouthwash."

34. *Necrosis.* Refers to circumscribed localized areas of cell or tissue death caused by almost any type of severe injury.

35. *Obtundent.* "Obtundent" is used synonymously with "topical analgesic." (See Part II. paragraph A.4 above—Analgesic (topical).)

36. *Oral mucosal analgesic.* An ingredient used in dental care drug products for topical application in the oral cavity to provide temporary relief of oral discomfort by an anesthetic or analgesic effect.

37. *Oral mucosal injury agent.* An agent which relieves oral soft tissue injury, e.g., by cleansing or promoting the healing or oral wounds (minor oral irritations).

38. *Oral mucosal protectant.* An agent which is a pharmacologically inert substance which forms an adherent, continuous, flexible, or semirigid coating when applied to the oral mucous membranes. The coating protects the irritated area from further irritation due to the activity of oral structures.

39. *Pharmacotherapeutic.* The Panel has classified ingredients into various pharmacotherapeutic groups according to the expected therapeutic effect at the intended site of action.

40. *Placebo.* An inactive substance or preparation used in controlled studies to determine the effectiveness of an agent presumed to be active. Generally, a placebo preparation will be identical to the test preparation except that the active or test ingredient will not be present.

41. *Professional labeling.* Drug usage directions for the use of a product intended for, and distributed only to, health care professionals.

42. *Prophylactic.* The term "prophylactic" indicates the prevention of disease. In this document, "prophylactic" is synonymous with "preventative."

43. *Sloughing.* A slough is a mass of dead tissue in, or cast out from, living tissue. Sloughing is the formation or separation of dead from living tissue.

44. *Systemic effect.* An effect related to the entire body as contrasted to a local effect which is an effect on one specific structure. In general, drugs which are absorbed into the blood stream can be assumed to exert systemic effects, although the desired and the observable sites of action may be fairly specific structures or organs.

45. *Teratogenicity.* The capacity of a drug to exert a harmful effect on a developing fetus. Agents which are suspected or known teratogens should not be taken during actual or suspected pregnancy.

46. *Tooth desensitizer.* "Tooth desensitizer" is synomymous with "dentin desensitizer." (See part II. paragraph A.20. above—Dentin desensitizer.)

47. *Topical analgesic (topical anesthetic).* In this report, "topical anesthetic" is used synonymously with "topical analgesic." See part II. paragraph A.4. above—Analgesic (topical).

### *B. General Comments*

The Panel recognizes that there is a consumer population which has an occasional need for OTC preparations to treat minor trauma or irritation which casuses inflammation of a transient nature to the gums or teeth. The Panel has classified such preparations as drug products for the relief of oral discomfort. The drugs within this classification have been subclassified into the following pharmacotherapeutic groups: (1) Agents for the relief of toothache, (2) oral mucosal analgesics, (3) oral mucosal protectants, and (4) tooth desensitizers. In addition, the Panel will discuss dental poultices as a dosage form.

1. *Agents for the relief of toothache.* Agents for the relief of toothache provide temporary relief of pain arising as a result of an open tooth cavity. A counterirritant may also be an agent for the relief of toothache. All agents for the relief of toothache except counterirritants are applied into an open tooth cavity. Counterirritants are applied in a dental poultice to the gingiva surrounding a tooth with a painful pulpitis. Agents for the relief of toothache have been on the market for a long period of time; they probably had their origin in empiric medicine.

The dental profession has voiced considerable concern about the safety and effectivenes of agents for the relief of toothache (Ref. 1). The Panel reviewed complaints about various dental products from a variety of sources. In brief, many dentists and dental organizations expressed concern that agents for the relief of toothache can have harmful effects and that their effectiveness is doubtful (Refs. 1 and 2).

After studying consultants' reviews and comments, and after reviewing the submissions and other pertinent

literature, the Panel came to the conclusion that because there may be a significant target population who could obtain temporary relief from some toothache medications, it would be helpful to have such medications, it would be helpful to have such medication available to the consumer.

2. *Oral mucosal analgesics.* Oral mucosal analgesics are surface or topical application to provide temporary relief of oral discomfort. Some injectable local anesthetics have surface anesthetic properties when applied in ointment, gel, or other topical dosage form. The most commonly used surface anesthetics for OTC dental use are benzocaine and butacaine. Benzocaine (ethylaminobenzoate) is very commonly used as a surface anesthetic; slow absorption makes it safe for use on wounds and mucous membranes (Ref. 3). Various aromatic principles and alcohols also have modest to intense surface anesthetic effects. Tainter (Ref. 4) found that phenol, benzyl alcohol, menthol, and chlorobutanol have topical anesthetic activity.

3. *Oral mucosal protectants.* Oral mucosal protectants are insoluble, pharmacologically inert substances that form adherent, continuous, flexible, or semirigid coats when applied to the oral mucous membranes (Ref. 5). These coatings help to protect the irritated areas of the mouth from further irritation from chewing, swallowing, and other mouth activity. When applied locally to the oral mucous membranes, they can provide temporary relief of discomfort of minor thermal or chemical burns, irritations, or ulcerations resulting from mechanical trauma and aphthous ulcerations (canker sores).

4. *Tooth desensitizers.* Tooth desensitizers are agents used to treat "hypersensitive" (ultrasensitive) dentin. This condition can develop when dentin is exposed to the environment of the oral cavity. The dentin, which contains the sensory apparatus of the tooth, is normally covered by either enamel (crown) or cementum (root). When the latter calcified structures are absent as a result of erosion, abrasion, removal by the dentist, a defect in the tooth, or some other cause, the resultant exposed dentin can become ultrasensitive to various stimuli. Temperature change, mechanical stimuli, and certain chemicals may then induce a painful response. The dentist may make the diagnosis of hypersensitive dentin if all carious lesions have received professional treatment, if there are no restorations causing the ultransensitive response, and if there are no symptoms suggestive of pulpal pathology. Even though the consumer cannot make this diagnosis without professional advice, it is still considered useful by the Panel to have tooth desensitizers available OTC for temporary use until a dentist can be seen or after a dentist has made a diagnosis of dental hypersensitivity and recommends the use of a tooth desensitizer. It is estimated that there is a significant target population with hypersensitive dentin which would use an OTC dentifrice for desensitization. (Ref. 6). Therefore, the Panel recommends that these products be made available to the public with a warning that, unless recommended by a dentist, the products are to be used for not more than 2 weeks. The labeling should include appropriate statements on the dangers of neglecting dental care. (See part II. paragraph C.4. below—Warnings).

5. *Dental poultices.* Dental poultices are topical dosage forms containing medication enclosed within a porous sack. When applied to the oral mucous membrane in the presence of moisture, the dental poultice releases the active ingredient.

Dental poultices are in many respects similar to externally applied cataplasms or poultices, one of the oldest classes of pharmaceutical preparations. These products are defined as being usually soft, mushy, or semiliquid preparations to be applied to the skin for the purpose of either stimulating a body surface or alleviating an inflamed area by supplying medicaments in the presence of moisture (Ref. 7). Poultices are reported to be applied for the purpose of drawing infectious materials from diseased tissues as a result of the absorptive qualities of the ingredients used (Ref. 8).

The Panel believes that there is a possibility of a dental poultice becoming accidentally lodged in the throat or in the respiratory tract if the user falls asleep with the poultice in place. The Panel recommends, therefore, that the label of the products carry the warning, "To avoid danger of choking do not leave a poultice in the mouth during periods of sleep."

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(8) Minutes of Advisory Review Panel on OTC Dentifrices and Dental Care Drug Products, 14th meeting, December 4 and 5, 1974.

### *C. Labeling for OTC Drug Products for the Relief of Oral Discomfort*

The Panel reviewed and concurs with the FDA's OTC drug labeling regulations (21 CFR 201.61 (a), (b), and (c) and 21 CFR 330.10(a)(4)(v)). Having reviewed all of the submitted labels of OTC drug products for the relief of oral discomfort, the Panel recommends that labeling include the following:

1. *Ingredients.* Dentifrice and dental care agents should contain only active ingredients plus such inactive ingredients as may be necessary for formulation. The label should state the name and quantity of each active ingredient in appropriate units to be specified later in each section of this document. The Panel encourages the use of metric units when possible.

The labeling must indicate the principal intended action of the active ingredient as well as the indication for use of the product. The Panel considers that the labeling for any product that contains an active ingredient for which no claim is made is misleading.

For various reasons, individuals may wish to avoid using certain inactive ingredients found in drug products. Such reasons include allergic reactions, previous idiosyncratic responses, safety concerns (whether valid or not), or personal preference. It is impossible to make a free choice in this regard unless all the components of drug products are listed on the labels. Therefore, this Panel strongly recommends that all inactive ingredients be listed on the label in descending order of quantity. However, the product should not imply or claim that its inactive ingredients have a therapeutic benefit.

The Panel recognizes that although full disclosure of flavoring and coloring ingredients is desirable, this may be impractical and confusing because of the large number of ingredients which may be involved. Thus, flavoring and coloring ingredients may be listed in accordance with present regulations for

labeling such ingredients in cosmetic products (21 CFR 701.3).

2. *Indications.* The indications for use of an oral mucosal protectant, tooth desensitizer, oral mucosal analgesic, or agent for the relief of toothache should be simply and clearly stated and should provide the user with a reasonable expectation of results to be anticipated from use of the product.

Statements of indications for use should be specific and confined to the conditions for which the product is recommended. No reference should be made, or implied, regarding the alleviation or relief of symptoms unrelated to the condition accepted as an indication for use of the product. Thus, a prominent and conspicuous statement must be made of general pharmacotherapeutic action. For example, drug products for the relief of oral discomfort should be labeled to indicate their usage, i.e., "agent for the relief of toothache," "oral mucosal protectant," "oral mucosal analgesic," etc.

The Panel concludes that drug products which have antiplaque, plaque control, or gingivitis claims are not currently appropriate for the OTC market because there is no general recognition of any such drug products as safe and effective for these indications at this time. Accordingly, the Panel recommends that such drug products and claims should be evaluated by FDA through the new drug application (NDA) procedure.

3. *Directions for use.* The directions for use should be clear, direct, and provide the user with sufficient information to permit safe and effective use of the product.

The label should include a clear statement of the usually effective minimum and, where applicable, maximum dose (or concentration if more appropriate) per time interval. If dosage varies with the consumer's age, the directions should be broken down by age groups. In appropriate instances, the usual directions may be followed by a statement recommending the supervision of a dentist or physician in the use of the product. The Panel will recommend specific directions for use under each drug statement in later sections of this document.

4. *Warnings.* Labeling of dental care products should include warnings against unsafe use, side effects, and adverse reactions. The Panel considers the following warnings necessary for the safe use of OTC drug products for the relief of oral discomfort.

a. *For all OTC drug products for the relief of oral discomfort.* (1) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(2) "Do not swallow."

(3) "Do not exceed recommended dosage."

b. *For all drug products for the relief of oral discomfort except for products containing tooth desensitizer active ingredients.*

"Not to be used for a period exceeding 7 days."

c. *For all drug products for the relief of oral discomfort except for products containing butacaine sulfate.*

"Children under 12 years of age should be supervised in the use of this product."

d. *For all drug products for the relief of oral discomfort containing butacaine sulfate.* (1) "Do not use in children under 12 years of age unless recommended by a dentist or physician."

(2) "Do not use more than one unit at a time."

(3) "Do not repeat except after 3 hours."

(4) "Do not exceed three doses daily."

e. *For all drug products for the relief of oral discomfort containing cresol.*

"Do not use in children under 6 years of age unless recommended by a dentist or physician."

f. *For all drug products for the relief of oral discomfort containing eugenol.*

"Do not use if you are allergic to eugenol."

g. *For all drug products for the relief of oral discomfort containing "caine" derivatives.*

"Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

h. *For OTC drug products containing oral mucosal analgesic active ingredients*—(1) *For oral mucosal analgesics (topical anesthetics) for teething pain.*

"Fever and nasal congestion are not symptoms of teething, and may indicate the presence of infection. If these symptoms persist, consult your physician."

(2) *For oral mucosal analgesics (topical anesthetics) in denture adhesive products.*

"See your dentist as soon as possible."

i. *For OTC drug products containing agents for the relief of toothache*—(1) *For all agents for the relief of toothache.*

(a) "A dentist must be seen as soon as possible whether or not the pain is relieved."

(b) "Toothaches and open cavities indicate serious problems which need prompt attention by a dentist."

(2) *For agents for the relief of toothache intended for use in an open tooth cavity.*

"Use only in teeth with persistent, throbbing pain."

(3) *For agents for the relief of toothache in a dental poultice dosage form.* (a) "Do not instill in tooth cavity."

(b) "Do not apply to irritated oral soft tissue. Use only on healthy tissue."

j. *For OTC drug products containing tooth desensitizer active ingredients.* (1) "Do not continue use beyond 2 weeks except under supervision of a dentist."

(2) "Sensitive teeth may indicate a serious problem which needs prompt care by a dentist."

(3) "See your dentist as soon as possible whether or not relief is obtained."

5. *Packaging.* The Panel recommends packaging restrictions for several OTC drug products for the relief of oral discomfort. Limitation of package size is recommended for the following products in view of safety considerations discussed elsewhere in this document.

a. Products containing benzoin preparations (benzoin tincture and compound benzoin tincture) should be packaged in well-closed containers of 30 mL or less and should have child-resistant caps.

b. Products containing benzyl alcohol should contain no more than 0.6 mL (30 mL of a 2-percent solution or 60 mL of a 1-percent solution) of benzyl alcohol in a container capable of maintaining stability of the product.

c. Products containing butacaine sulfate should be packaged in single-use units to contain no more than 30 mg of butacaine sulfate each with no more than six units per package.

d. Products containing capsicum for use as a counterirritant should be packaged to contain no more than eight applications.

e. Fluoride-containing dentifrices should not contain more than 260 mg total fluorine.

D. *Principles Applicable to Combination Products.*

1. *General combination policy.* The Panel believes that the interests of the consumer are best served by exposing a user of OTC drugs to the fewest ingredients and the lowest dosage that will provide a satisfactory level of effectiveness. Single-component OTC drugs are preferable because they afford a lower risk of undesirable side effects and permit more precise treatment of individual symptoms. The Panel recognizes that there may be a reason for combining active ingredients in certain OTC drugs; however, such combinations must be based on a sound

and logical scientific rationale. The Panel applied the OTC drug review regulation (21 CFR 330.10(a)(4)(iv)) in developing a combination policy for dentifrice and dental care drug products.

The Panel recommends that a product may contain no more than two Category I dentifrice and dental care agent active ingredients that meet the regulatory requirements as well as the criteria adopted by the Panel, together with suitable inactive ingredients, provided that (a) the active ingredients are safe and effective and do not antagonize the therapeutic usefulness of each other, (b) the inactive ingredients are safe and do not interact with or otherwise inhibit the effectiveness of the active ingredients, (c) there is a significant target population that has a single symptom or concurrent symptoms and can thus benefit from use of the combination, (d) use of the combination does not decrease the safety due to adverse effects over use of the single ingredient, and (e) the combination contains adequate directions for use and is labeled with adequate warnings against unsafe use.

The Panel found that some OTC dentifrice and dental care drug products contain combinations of active ingredients both from the same and from different pharmacotherapeutic groups. The Panel is not convinced that combinations containing two or more relief of oral discomfort agents from the same pharmacotherapeutic group with the same mechanism of action would be more effective than the single ingredient alone. Further, combining full therapeutic concentrations of two or more ingredients for the relief of oral discomfort from the same pharmacotherapeutic group with the same mechanism of action may incur unwarranted additional risk.

The alternative to combining two ingredients from the same pharmacotherapeutic class with the same mechinism of action at each ingredient's effective dose is to combine subtherapeutic doses of the ingredients on the theory that such a combination will reduce the risk of side effects or adverse reactions. The Panel prefers full concentrations of single ingredients because it is not aware of any data to support the use of two ingredients with the same mechanism of action in subtherapeutic doses. Combinations containing ingredients of the same pharmacotherapeutic group with the same mechanism of action at less then the minimum effective concentration for any one of the ingredients are, therefore, classified in Category II.

The Panel recognizes that relief of oral discomfort drug products have also been combined with active ingredients from other pharmacotherapeutic groups. The Panel has reviewed and classified combinations of active ingredients for the relief of oral discomfort with active ingredients for the treatment of oral mucosal injury, as discussed below.

The Panel is aware that active ingredients for the relief of oral discomfort have also been combined with oral antiseptic active ingredients, which have been reviewed by the Advisory Review Panel on OTC Oral Cavity Drug Products, and with denture adhesives, which are being reviewed by the Bureau of Medical Devices. These combination products were reviewed and classified by this Panel as to their rationale for concurrent therapy.

The same general principles apply when an active ingredient from a different pharmacotherapeutic group reviewed by another OTC drug advisory panel is combined with an active ingredient of a pharmacotherapeutic group reviewed by this Panel. The rationale for such combinations should be evaluated by FDA according to the combination policy set forth in the reports of both panels.

2. *Limitation of ingredients in combination products.* The Panel recommends that not more than two dentifrice and dental care agent active ingredients be included in any combination product because the addition or more ingredients would increase the risk to the consumer without increasing the benefit.

3. *Labeling of active ingredients.* Labeling for the combination product must conform to the recommended labeling for each active ingredient, and must specify any additional information such as drug interactions or adverse reactions that occur with the combination products, but not with the individual ingredients used alone. The labeling for a Category I combination product should stress that the product should be used only when all symptons are present. The product's labeling should not induce the consumer to take a combination drug when a single entity is appropriate and effective. The consumer should be adequately informed, through the labeling, of the total therapeutic capabilities of the product.

4. *Criteria for Category I combination products.* The Panel recommends the following general criteria for Category I combination drug products for the relief of oral discomfort.

The Panel recommend that each claimed active ingredient in a combination product must make a statistically significant contribution to the claimed effect or effects of the product.

Two Category I active ingredients from different pharmacotherapeutic groups may be combined to treat different symptons concurrently if each Category I active ingredient is present within its established dosage range; the combination is rational; there is a significant target population that suffers from the concurrent symptons; and the combination is as safe and as effective as each individual active ingredient used alone.

5. *Category I combination drug products for the relief of oral discomfort.* The Panel recommends that the following combinations be classified as Category I for the relief of oral discomfort.

a. *Combination of two agents for the relief of oral discomfort (an oral mucosal protectant and an oral mucosal analgesic).* One Category I oral mucosal protectant may be combined with one Cagetory I oral mucosal analgesic. An oral mucosal protectant protects the affected area from a pain stimulus, and an oral mucosal analgesic provides relief in pain. These two agents complement each other when used in the same dosage form, and both are intended to remain on the wound.

b. *Combinations of an agent for the relief of oral discomfort with an oral antiseptic.* (Reviewed by the Advisory Review Panel on OTC Oral Cavity Drug Products.)

(1) *Oral mucosal protectant and an oral antiseptic.* The Panel finds that this combination is rational and will provide the patient with additional protection against further irritation and infection. The oral mucosal protectant will provide a coating over the wound and hold the antiseptic agent in place where it can act most effectively.

(2) *Oral mucosal analgesic and an oral antiseptic.* The Panel finds that this combination is rational. Pain may frequently accompany minor oral wounds, and treating the discomfort and preventing possible infection concurrently is a convenient and reasonable approach to therapy.

(3) *Oral mucosal protectant, oral mucosal analgesic, and an oral antiseptic.* The Panel finds that this combination is rational. An oral mucosal analgesic provides relief of pain, the oral mucosal protectant provides a coating over the wound, and the antiseptic agent is held in place where it can act most effectively.

c. *Combination of an agent for the relief of oral discomfort and a denture adhesive.* (Under review by the Bureau of Medical Devices.)

*Oral mucosal analgesic and a denture adhesive.* The Panel finds that this combination is rational. Immediate dentures, particularly, may be uncomfortable or painful in some instances. Combining an oral mucosal analgesic with a denture adhesive may enable the denture wearer to benefit from the analgesic action, while the adhesive helps to secure the dentures, and both actions increase the comfort of the user.

6. *Criteria for Category II combination products.*

The Panel recommends the following criteria for Category II combination drug products for the relief of oral discomfort.

a. A combination is Category II if a Category II active ingredient or Category II labeling is present in the combination product.

b. A combination product containing Category I or Category III active ingredients from the same pharmacotherapeutic group with the same mechanism of action is classified as Category II.

c. A combination product containing active ingredients from different pharmacotherapeutic groups is classified as Category II if it includes any ingredient in less than the minimum effective concentration established by the Panel.

d. If a combination contains an active ingredient or other condition that has not been reviewed by this or any other OTC drug advisory review panel, such ingredient or condition is Category II and the resulting combination then becomes Category II.

e. A combination product is classified as Category II if it includes more than two dentifrice and dental care agent active ingredients.

f. A combination product is classified as Category II if it contains active ingredients from more than one pharmacotherapeutic group and there is not a significant target population that has a concurrent need for a drug from each of these groups.

g. A combination of two Category I active ingredients from different pharmacotherapeutic groups is Category II if the ingredients cannot be combined because of chemical or physical formulation problems that would result in decreasing the safety or effectiveness of the individual ingredients.

7. *Category II combination drug products for the relief of oral discomfort.* The Panel recommends that the following combinations be classified as Category II for the relief of oral discomfort.

a. *Combinations of two agents for the relief of oral discomfort*—(1) *Oral mucosal protectant and an agent for the relief of toothache.* The Panel finds no rationale for such a combination. These two agents are intended to be applied at different sites in the oral cavity and to treat symptoms resulting from different etiologies. Further, if administered in a combination product, the oral wound protectant might obstruct the tooth cavity and prevent the escape of gases and fluids. The Panel considers such an obstruction to be detrimental and dangerous to the health of the consumer.

(2) *Oral mucosal protectant and a counterirritant.* The Panel finds no rationale for such a combination; such ingredients are, in fact, therapeutically antagonistic. By definition, a counterirritant is irritating, and such an agent should not be applied to injured tissue either alone or in combination with a wound protectant.

(3) *Oral mucosal protectant and a tooth desensitizer.* The Panel finds no rationale for such a combination. These pharmacotherapeutic agents are intended to be applied at different sites and to treat symptoms resulting from different etiologies.

(4) *An agent for the relief of toothache intended to be used in an open tooth cavity and a counterirritant.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and should never be placed in the tooth cavity. Such irritating agents therefore should not be used in combination with an agent intended to be used in an open tooth cavity to provide toothache relief.

(5) *An agent for the relief of toothache and a tooth desensitizer.* The Panel finds no rationale for such a combination. These pharmacotherapeutic agents are intended for application to different sites and to treat symptoms resulting from different etiologies.

(6) *Oral mucosal analgesic and an oral mucosal analgesic, both from the same group with the same mechanism of action.* The Panel concludes that any combination of two oral mucosal analgesics from the same group with the same mechanism of action, at full or less than full therapeutic concentrations, is Category II. This includes the combination of two "caine" or the combination of two aromatic analgesics. The weight of scientific evidence is against such combinations (Ref. 1).

(7) *Oral mucosal analgesic and a tooth desensitizer.* The Panel finds no rationale for such a combination. These pharmacotherapeutic agents are intended to be applied at different sites, and are for the relief of different types of painful symptoms with different etiologies.

(8) *A counterirritant and a counterirritant.* The Panel finds no rationale for such a combination and prefers a single-ingredient product.

(9) *A counterirritant and a tooth desensitizer.* The Panel finds no rationale for such a combination. These pharmacotherapeutic agents are intended to be applied at different sites. Irritating chemicals should not be applied to exposed dentin.

b. *Combinations of an agent for the relief of oral discomfort with an oral mucosal injury agent*—(1) *Oral mucosal protectant and an oral wound cleanser.* The Panel finds no rationale for such a combination. An oral mucosal protectant forms a protective film over the area to which it is applied. The use of an oral wound cleanser in the same dosage form with an oral mucosal protectant would result in the cleanser removing the protectant from the affected area, thus making the protectant ineffective.

(2) *An agent for the relief of toothache and an oral wound cleanser.* The Panel finds no rationale for such a combination. If an agent for the relief of toothache is administered in the same dosage form with an oral wound cleanser, the agent for the relief of toothache will be removed from its site of action when the oral wound cleanser is expectorated and, thus, before it has had an opportunity to exert its intended pharmacotherapeutic effect. These two pharmacotherapeutic agents are intended to be used at different sites in the oral cavity.

(3) *Oral mucosal analgesic and an oral wound cleanser.* The Panel finds no rationale for such a combination. If an oral mucosal analgesic is administered in the same dosage form with an oral wound cleanser, the oral mucosal analgesic will be removed from its site of action when the oral wound cleanser is expectorated. These two pharmacotherapeutic agents are intended to be used sequentially and not at the same time.

(4) *Counterirritant and an oral wound cleanser.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and such an agent should not be used when cleansing a wound.

(5) Tooth desensitizer and an oral wound cleanser. The Panel finds no rationale for such a combination.

(6) *An agent for the relief of toothache and an oral wound-healing agent.* An oral wound-healing agent is intended for use on mucosal tissue, not on tooth pulp. An agent for the relief of toothache is intended for use on irreversibly damaged pulp and should only be used when there is no possibility that the pulp injury is reversible. Hence, an oral

wound-healing agent would confer no benefit when applied to tissue that has no potential for healing.

(7) *Counterirritant and an oral wound-healing agent.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and such an agent should not be used on a healing wound.

(8) *Tooth desensitizer and an oral wound-healing agent.* The Panel finds no rationale for such a combination. These two pharmacotherapeutic agents are intended to be used at different sites in the oral cavity.

(9) *Oral mucosal protectant and a peroxide-containing oral wound-healing agent.* The Panel finds no rationale for such a combination. If an oral mucosal protectant is administered in the same dosage form with a peroxide-containing oral wound-healing agent, the bubbling action of the peroxide would remove the protectant from the site of action before it has had an opportunity to exert the intended pharmacotherapeutic effect.

(10) *Oral mucosal analgesic and a peroxide-containing oral wound-healing agent.* The Panel finds no rationale for such a combination. If an oral mucosal analgesic is administered in the same dosage form with a peroxide-containing oral mucosal analgesic, the bubbling action of the peroxide would remove the analgesic from the site of action before it has had an opportunity to exert the intended pharmacotherapeutic effect.

c. *Combinations of an agent for the relief of oral discomfort with an oral antiseptic.* (Reviewed by the Advisory Review Panel on OTC Oral Cavity Drug Products.)

(1) *An agent for the relief of toothache and an oral antiseptic.* The Panel finds no rationale for such a combination. The oral antiseptic will not contribute to the relief of toothache, nor is any infection within the tooth controllable by applying an antiseptic.

(2) *A counterirritant and an oral antiseptic.* The Panel finds no rationale for such a combination. A counterirritant must only be applied to normal oral mucosa. Since no infection is present at the site of use, no antiseptic is needed.

(3) *A tooth desensitizer and an oral antiseptic.* The Panel finds no rationale for such a combination. A tooth desensitizer is applied by brushing and is not applied at the site of an infection. It would be irrational either to use an antiseptic in the absence of any infection or to apply an antiseptic in a dosage form that must be brushed onto the site of application.

d. *Combinations of an agent for the relief or oral discomfort with a denture adhesive.* (Under review by the Bureau of Medical Devices.)

(1) *An oral mucosal protectant and a denture adhesive.* The Panel finds no rationale for such a combination. An oral mucosal protectant forms a film over the area to which it is applied. Such a film would interfere with the action of the adhesive. The added thickness of the oral wound protectant would also interfere with the fit of the dentures and could be expected to cause further injury or irritation as a result.

(2) *An agent for the relief of toothache and a denture adhesive.* The Panel finds no rationale for such a combination. These two agents are intended to be applied at different sites in the oral cavity.

(3) *A counterirritant and a denture adhesive.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and such an agent should not be used under dentures.

(4) *A tooth desensitizer and a denture adhesive.* The Panel finds no rationale for such a combination. These two agents are intended to be applied at different sites in the oral cavity.

8. *Criteria for Category III combination products.* The Panel recommends the following criteria for Category III combination drug products for the relief of oral discomfort.

a. If a Category III active ingredient or other condition is present in a combination product containing no Category II ingredient or labeling the combination is classified as Category III.

b. If two agents for the relief of oral discomfort from the same pharmacotherapeutic group, but with different mechanisms of action, are present in a combination drug product, that combination is classified as Category III.

9. *Category III combination drug products for the relief of oral discomfort.* The Panel recommends the following combinations be classified as Category III for the relief of oral discomfort.

a. *Combination of two agents for the relief of oral discomfort*—(1) *Oral mucosal protectant and an oral mucosal protectant.* The Panel did not review any data relating to such combinations. However, the Panel believes that there may be a rationale for combining two such agents. Data must be generated to establish that each ingredient makes a contribution to the claimed effect without decreased effectiveness or safety.

(2) *A tooth desensitizer and a tooth desensitizer.* There may be a rationale for combining two such agents. However, the data reviewed by the Panel relating to such combinations did not establish that each ingredient makes a contribution to the claimed effect.

b. *Combinations of an agent for the relief of oral discomfort with certain oral mucosal injury agents*—(1) *Oral mucosal protectant and an oral wound healing agent.* These two types of agents may be combined provided testing is performed to establish that the oral mucosal protectant does not interfere with the action of the oral wound healing agent. The protectant will hold the oral wound healing agent in place at the site of the wound, and will also protect the wound from further injury and irritation.

(2) *Oral mucosal analgesic and an oral wound healing agent.* The oral mucosal analgesic will provide relief of the symptoms of pain or discomfort while the oral wound healing agent promotes healing.

(3) *Two agents for the relief of toothache acting by different mechanisms.* Agents for the relief of toothache may act by different mechanisms. For example, benzocaine and butacaine are Category III agents for the relief of toothache and would act by producing surface anesthesia, while eugenol is a Category I agent for the relief of toothache and probably obtunds toothache by a different mechanism (Ref. 2).

(4) *An agent for the relief of toothache and an oral mucosal analgesic.* Since some oral mucosal analgesics are also agents for the relief of toothache, they may be combined under the conditions described under (3) above for the relief of toothache but not for use as oral mucosal analgesics.

(5) *An oral mucosal analgesic and a counterirritant.* The only counterirritant acceptable to the Panel in Category III is capsicum. Capsicum is used to provide relief of toothache pain in a poultice dosage form applied between the cheek and the gum, and should only be applied to intact, nonirritated mucous membrane. Capsicum has been combined in poultices with the oral mucosal analgesic benzocaine.

(6) *Two oral mucosal analgesics acting by different mechanisms.* Oral mucosal analgesics may act by different mechanisms, e.g., benzocaine (a "caine") and phenol (an aromatic). Therefore, it may be rational to combine them at full or less-than full dosage.

c. *Combinations of an oral mucosal protectant with an oral mucosal analgesic claiming a prolonged duration of action.*

Oral mucosal protectants may hold an oral mucosal analgesic in contact with the affected area for a longer period of

time than if the oral mucosal analgesic were applied as a single active ingredient. This effect, however, has not been proven for any combination.

Data must be generated to establish that such a combination significantly prolongs the duration of action of the oral mucosal analgesic without decreasing the safety or effectiveness of either ingredient. Any claim of this longer duration of action due to the combination must be proven, and the Panel recommends that such a claim be classified as Category III.

**References**

(1) Adriani, J., and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association*, 188:711–716, 1964.

(2) Bender, I. B., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 14th meeting, October 16–17, 1974.

*E. Statement on Category III Testing Procedures*

1. *Comments on study design.* The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III active ingredient into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

Experimental design should take into account the need to include a sufficient number of subjects or trials so as to provide meaningful conclusions which can be supported by appropriate statistical analysis. The selection of appropriate subjects or patients can be a major importance when the effect of a drug in a specific illness or symptom is under study.

Some bias may exist in all situations wherein the subject, the observer, or both make a judgment as to the nature or magnitude of a response. Biological factors also contribute to variation in response between individuals in a given study sample. Although bias and biological variation cannot be eliminated, their effect on the outcome of an experiment can be minimized by adopting a "double-blind, placebo-controlled" or other suitably blinded design. In such a design, one group of subjects receives a placebo so that the placebo response, unmodified by the conditioning of the test, can be established. Whenever possible, neither the subjects nor the observer should be able to distinguish the identity of the preparations under test. This requires that the test preparations and placebos be indistinguishable in regard to shape, color, odor, and taste. However, in the case of preparations containing active volatile agents or substances which affect sensory perception, it is impossible to make the placebo indistinguishable from active ingredients. When a placebo is used for comparison, the medication should exert a quantitatively positive effect which is statistically significant when compared to the placebo. The level of statistical significance which is acceptable is described under each Category III protocol. (See paragraph C. of parts III., IV., V., and VI. below—Data Required for Evaluation.)

It is often desirable to include, as a positive control, a standard drug which is known to exert a significant effect against the relevant symptoms being tested. When a standard drug is used for comparison, the test medication should be at least equivalent to the standard.

Finally, the inclusion of two or more dose levels (or concentrations) of the drug under test may be desirable in order to provide an estimate of an effective therapeutic dose range which is free from undesirable side effects. If a crossover design is utilized, i.e., each subject serves as his or her own control, the sequence in which the placebo, standard, and test drugs are administered should be randomized and a sufficient "wash-out period" between tests should be permitted.

Wherever possible, objective measurements should be made in preference to subjective judgments. However, subjective measurements may be required if relevant to the symptom or symptom complex for which the drug under test is to be used.

2. *Testing period provided for Category III conditions.* The Panel has determined that the available data are insufficient (Category III) to classify some conditions either as Category I or Category II. Such conditions are permitted to remain on the market, or to be introduced into the market, after the date of publication of the final monograph in the **Federal Register**, provided that FDA receives notification of testing in accordance with § 330.10(a)(13) (21 CFR 330.10(a)(13)). The Panel recommends that Category III conditions should be tested within 2 years except as noted for specific pharmacotherapeutic groups.

3. *Testing guidelines for Category III combination products.* The Category III active ingredients for the labeling indication claims must be tested in accordance with the evaluation protocol specified for that particular pharmacotherapeutic classification. If, when tested alone, the Category III ingredient or ingredients can be shown to be safe and effective in accordance with the standards for evaluation established in the protocols, it will then qualify for Category I status. The combination will then contain only Category I active ingredients, but still must be tested to prove that each ingredient makes a contribution to the product's claimed effect(s).

An acceptable test procedure will be one in which the proposed combination and each of the individual active ingredients at the proposed dosage level in the combination are evaluated, all in the same study, and compared to a placebo for effectiveness against the relevant labeling claim. In this way it can be shown whether or not each active ingredient in the combination makes a contribution toward effectiveness without incurring an unnecessary decrease in safety.

*F. Drug Misuse and Abuse*

The potential for development of drug tolerance and addiction due to the use of dentifrices and dental care agents, even when the patient is on an unsupervised regimen, does not seem to exist. However, the Panel believes that misuse of dental care agents occurs when an agent tends to give the subject a false sense of security, thereby diminishing his desire to seek professional advice. When this possibility exists, the label warnings should alert the patient to this danger.

Several products, such as denture adhesives combined with oral mucosal analgesics and agents for the relief of toothache, discussed elsewhere in this document, are excellent examples of drug products which might be subject to misuse. The problem becomes especially acute when signs of an infection or other symptoms are subdued but the underlying cause is not corrected or if a subject, needing professional dental care, uses an OTC dental care drug product to enable him or her to postpone the needed care. Labeling of OTC dentifrice and dental care drug products should include warnings against possible misuse of the specific ingredients.

*G. Pediatric Considerations*

The Panel reviewed the conditions under which dental care products can be safely used by children. Children are defined by the Panel as persons under 12 years of age. Many of the active ingredients reviewed by the Panel as drug products for the relief of oral discomfort have different indications, dosages, and directions for different age groups. For specific information on the labeling of individual active ingredients, see the labeling discussions elsewhere in this document. (See paragraph B.1. of

parts III., IV., V., and VI. below—Category I Labeling.)

The Panel considered the acute and chronic toxic effects of fluoride ingestion in determining whether drug products containing fluoride can be safely used by children. The Panel's recommendations for the use of these products by children are included in the preamble to the proposed monograph on anticaries drug products in the section entitled "Pediatric Considerations" (45 FR 20673; March 28, 1980). The proposed monograph on anticaries drug products (hereinafter referred to as the anticaries report) was published in the **Federal Register** of March 28, 1980 (45 FR 20666). The panel's recommendation concerning package size limitations and child-resistant closures for anticaries drug products are equally applicable to fluoride drug products used as tooth desensitizers.

Package size limitations have also been recommended for benzoin preparations and benzyl alcohol. The Panel recommends that benzoin preparations, which are Category I oral mucosal protectants, be packaged in containers of not more than 30mL compound benzoin tincture or 30 mL benzoin tincture and that the packages have child-resistant closures.

The Panel recommends that benzyl alcohol, which is a Category III oral mucosal analgesic and an agent for the relief of toothache, be packaged in containers which contain no more than 0.6 mL of benzyl alcohol. Animal studies suggest that ingestion of benzyl alcohol (1 mL/kg) may be fatal (Ref. 1). Package sizes that will provide more than 30 mL of a 2-percent solution of 60 mL of a 1-percent solution are unnecessary and may be a potential risk for accidental ingestion by young children.

Benzocain was reviewed by the Panel and is recommended for classification as a Category I oral mucosal analgesic and a Category III agent for the relief of toothache. The Panel is aware that benzocaine in high doses may cause methemoglobinemia, because it can interfere with the reconversion of methemoglobin to hemoglobin (Refs. 2 and 3.) Most reported systemic reactions reviewed by the Panel were in infants under 6 months of age (Refs. 4 throught 7). Infants may be more susceptible due to a deficiency of DPNH (diphosphopyridine nucleotide)-dependent methemoglobin reductase which protects against methemoglobin-inducing foreign compounds (Ref. 7). Infants under 4 months of age, who may have not as yet developed sufficient quantities of the reductase, develop methemoglobinemia more easily than older children and adults. The Panel has, therefore, recommended that infants under 4 months of age should not be treated with benzocaine except under the advice and supervision of a dentist or physician. No specific warning concerning methemoglobinemia is considered necessary.

The Panel has also recommended that children under 12 years of age should be supervised in the use of benzocaine-containing dental products.

**References**

(1) Macht, D. I., "A Pharmacological and Therapeutic Study of Benzyl Alcohol as a Local Anesthetic," *Journal of Pharmacology and Experimental Therapeutics,* 11:263–279, 1918.

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(3) Swinyard, E. A., "Local Anesthetics," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 987, 1975.

(4) Hughes, J. R., "Infantile Methemoglobinemia Due to Benzocaine Suppository," *Journal of Pediatrics,* 66:797–799, 1965.

(5) Peterson, H. C., "Acquired Methemoglobinemia in an Infant due to Benzocaine Suppository," *New England Journal of Medicine,* 263:454, 1960.

(6) Bloch, A., "More on Infantile Methemoglobinemia Due to Benzocaine Suppository," *Journal of Pediatrics,* 67:509–510, 1965.

(7) Wolff, J. A., "Methemoglobinemia Due to Benzocaine," *Pediatrics,* 20:915–916, 1957.

*H. Inactive Ingredients*

The Panel is aware of the need for the inclusion of inactive ingredients in OTC drug products for the relief of oral discomfort. Preferably, these should be limited to agents that are considered necessary such as abrasives, preservatives, aromatics, vehicles, colorants, sweeteners, antioxidants, buffers, and agents required for particular dosage forms.

The Panel did not undertake an extensive review of inactive ingredients, because it is the view of this Panel that the safety and the advisability of including specific inactive ingredients in drug products should be reviewed by an appropriate Panel. Since many of these ingredients are used in the formulation of many drug products other than those reviewed by this Panel, it is not appropriate that they be dealt with specifically and solely in relation to dentifrices and dental care agents for the relief of oral discomfort.

The Panel recommends that in view of the inactive ingredients, such as sodium lauryl sarcosinate, which have caused oral mucosal irritation, the final formulation of OTC drug products for the relief of oral discomfort should be shown to be safe and nonirritating. Monitoring of consumer complaints should detect, at an early stage, irritation or allergic manifestations not detectable in animal studies.

*I. Single Active Ingredient Products*

The Panel has discussed dental combination products earlier in this document. (See part II. paragraph D. above—Principles Applicable to Combination Products.) The Panel believes there are some combinations which may be rational for concurrent therapy of multiple symptoms for a significant portion of the target population. However, for the individual who has only one symptom and who may need only one ingredient, single active ingredients afford the opportunity to selectively treat such a condition.

Great variability with regard to side effects induced by drugs is seen among patients. Although these effects and the drugs producing them are sometimes familiar to dentists, physicians, and pharmacists, when the ingredient is present in a combination, it may be difficult to identify the ingredient causing the side effect. Furthermore, use of fixed combinations for the treatment of a particular symptom, where a single ingredient product would be safe and effective, exposes the consumer to additional risk of side effects, idiosyncratic reactions, and allergenicity without added benefit. These difficulties are largely avoided with single active ingredients, which many dentists and pharmacists prefer to recommend. There was agreement among Panel members that the availability of products containing single active ingredients would provide increased opportunity for the public and health professionals to select products appropriate to treat the symptoms.

*J. General Statements on the Determination of Safety and Effectiveness for OTC Dental Products*

The Panel evaluated the safety and effectiveness of OTC dental active ingredients as well as proper dosage ranges for OTC drug use. In reviewing the scientific literature for these ingredients. the Panel evaluated the available data as to whether or not the ingredient was safe and effective. Among those agents determined to be safe and effective, the Panel did not attempt to determine the drugs of choice for any particular indication.

1. *Determination of safety.* In deciding on the safety of a drug or combination of drugs for the intended use, both animal and human studies were considered. The animal data were usually related to

levels of the drug that might cause death or serious adverse effects on vital tissues such as the bone marrow, liver, and kidneys. Also, the possibility that the drug might cause adverse effects on teeth or irritation of the oral mucosa was evaluated. Animal studies were helpful in establishing benefit-to-risk ratios for ingredients which are commonly used.

Major attention was paid to information related to adverse drug effects in humans, both adults and children. A knowledge of the toxicology of the drug or drugs under consideration both in animal studies and from human experience makes it possible to look specifically for adverse effects in one or more organs or systems. For example, manufacturers of topical anesthetics were required to show that the ingredients used in their products were safe when such ingredients were used in effective concentrations.

It was desirable that there be studies in which the drug was evaluated in its final composition and compared to its vehicle control. However, there were times when the Panel was called upon to make judgments without benefit of controlled pharmacological studies, since they were not available for some ingredients.

2. *Determination of effectiveness.* In determining effectiveness for the intended use. the Panel considered separately each pharmacotherapeutic group under review although certain general principles apply to all groups.

In terms of effectiveness, animal studies were seldom very helpful since it is difficult to find animal models which closely mimic the course of oral diseases and conditions in humans.

Major attention was paid to clinical studies, especially where the double-blind technique could be employed. The inclusion of a placebo as a comparison was considered desirable and comparison of the agent with a known standard was also considered useful.

Studies utilizing objective measurements, proper controls, and statistical analysis carried considerable weight in the Panel's decision to place an ingredient in Category I. Clinical experience of a general nature, if documented by qualified experts, added somewhat to the final decisions.

The Panel recognizes the extensive marketing history of many dental preparations. Members of the drug industry presented data to the Panel summarizing their marketing history and consumer complaint information. The effectiveness of such products may never have been subjected to scientific investigation even though the products have been marketed for many years. Apparent consumer acceptance and testimonial data used by many manufacturers as the sole evidence of effectiveness and safety were not acceptable to the Panel. When claims of effectiveness were supported solely by outdated experimental methodology, this evidence for effectiveness was also considered unacceptable.

The Panel took into account the marketing experience of manufacturers as stated in their submissions. Although the Panel found these data helpful, marketing experience neither overruled nor substituted for the Panel's other sources of knowledge of safety, effectiveness, and rationale for such products.

SUMMARY OF THE PANEL'S CATEGORIZATION OF ACTIVE INGREDIENTS

| Active ingredients | Oral mucosal protectant | Agent for the relief of toothache | Tooth desensitizer | Oral mucosal analgesic | Counter-irritant |
|---|---|---|---|---|---|
| Benzocaine | | III(E) | | I. | |
| Benzoin preparations (benzoin tincture and compound benzoin tincture) | I. | | | | |
| Benzyl alcohol | | III(SE) | | III(SE) | |
| Butacaine sulfate | | III(SE) | | I. | |
| Camphor | | | | III(SE) | |
| Capsicum | | II(SE) | | | III(E). |
| Citric acid and sodium citrate in poloxamer 407 | | | III(E) | | |
| Creosote | | III(SE) | | | |
| Cresol | | III(SE) | | III(SE) | |
| Eugenol preparations (85 to 87 percent eugenol in clove oil or a bland, fixed oil) | | I. | | | |
| Eugenol (1 to 84 percent) | | III(E) | | | |
| Fluoride preparations (sodium fluoride, sodium monofluorophosphate, and stannous fluoride) | | | III(E) | | |
| Formaldehyde solution | | | III(E) | | |
| Menthol | | II(S) | | | |
| Methyl salicylate | | II(SE) | | II(SE) | |
| Myrrh, fluidextract | III(SE) | | | | |
| Phenol preparations (phenol and phenolate sodium) | | III(SE) | | I. | |
| Potassium nitrate | | | III(E) | | |
| Sodium fluoride, strontium chloride, and edetate disodium | | | II(SE) | | |
| Strontium chloride | | | III(E) | | |
| Thymol preparations (thymol and thymol iodide) | | III(E) | | III(E) | |

(S)=placed in indicated category for safety considerations.
(E)=placed in indicated category for effectiveness considerations.
(SE)=placed in indicated category for both safety and effectiveness considerations.

## III. Agents for the Relief of Toothache

### *A. General Discussion*

Agents for the relief of toothache provide temporary relief of pain arising as a result of an open tooth cavity. All agents for the relief ot toothache, except counterirritants, are applied into an open tooth cavity. Counterirritants are applied in a dental poultice to the gingiva surrounding a tooth with a painful pulpitis. Agents for the relief of toothache have been on the market for a long period of time; they probably had their origin in empiric medicine.

1. *Agents for the relief of toothache applied into an open tooth cavity.* It is now known that the dental pulp is very susceptible to irritation. Some causes of irritation are dental caries, excessive heat, and placement of irritating chemicals or filling materials in a deep cavity. Irritation causes inflammation in the pulp which can be divided into reversible and irreversible stages. During the reversible stage, the application of medication resulting in added irritation or dehydration of dentin may cause the damage of the pulp to reach the irreversible stage, rendering the tooth nonviable. Dehydration is damaging because it increases the permeability of the dentinal tubular contents. Thus, in general, any agent which irritates or dehydrates dentin is considered unsafe if applied during the reversible stage of pulp disease.

The dental profession has voiced considerable concern about the safety and effectiveness of agents for the relief of toothache (Ref. 1). The Panel

reviewed complaints about various dental products from a variety of sources. In brief, many dentists and dental organizations expressed concern that agents for the relief of toothache can have harmful effects and that their effectiveness is doubtful (Refs. 1 and 2).

The Panel called upon two expert consultants to provide their opinions on agents for the relief of toothache. These consultants were not in complete agreement; however, their opinions, based on their own and others' research and practice, were very helpful to the Panel (Refs. 3 and 4).

After studying the consultants' reviews and comments, and after reviewing the submissions and other pertinent literature, the Panel came to the following conclusions:

a. Most toothache remedies are very caustic preparations which will burn the oral mucosa. These burns heal rapidly so the consequences of this adverse effect are not severe. Of greater concern is the effect of these irritant chemicals on dentin and viable dental pulp.

b. The systemic effect of toothache remedies is generally not considered to be of consequence since only minute amounts of the drugs are used. Corticosteroids, which do have systemic effects, are limited to use by the dentist or physician. The Panel recognizes that any drug to which the subject is intolerant or allergic may be harmful even when applied in small quantities.

c. The main effect of OTC agents for the relief of toothache is probably as a placebo. Most of these preparations have a "medicinal" taste and smell and are irritants. These properties distract the patient and may provide some psychological feeling of benefit, but the major problems of deep caries, pulpitis, and infection remain untreated.

c. Irritants or agents instilled in the tooth cavity which excessively dehydrate the tooth structure (such as high concentrations of alcohols) can do harm to any pulp which as reversible damage, but cannot do further injury to the irreversibly damaged pulp. Ethyl alcohol above 20 percent is considered to be an irritant to the dental pulp and, therefore, should not be used above 20 percent in agents for the relief of toothache which are to be used in an open tooth cavity.

It is irrational to place a substance into a tooth cavity which may occlude the opening through which an abscess may drain allowing fluid and gas to escape. Cotton soaked with medication, waxes, or gums are occulsive agents. Agents which harden and form a filling, such as sandarac, may be especially detrimental. Occulsion of the cavity may intensify pain and promote the spread of infection to deeper tissues. Agents which occlude the cavity are, therefore, unacceptable.

The Panel recognizes that the ingredients beeswax and sandarac are inactive. However, the Panel feels that the use of occlusive agents such as these in a tooth cavity for the relief of toothache pain exposes the consumer to unnecessary safety risks. The Panel recommends that agents for the relief of toothache shall not contain any agent which acts as a physical barrier and does not permit the escape of fluids and gases from a degenerating pulp (Refs. 5 and 6). Blockage of the drainage from a cavity by ingredients such as beeswax and sandarac may result in increased pain and possible spread of infection.

Beeswax can act as a physical barrier in the tooth cavity. Sandarac is a resin which is soluble in alcohol, but insoluble in water. It is utilized as a component of certain cavity varnishes for professional application in dentistry. In OTC products for the relief of toothache, sandarac in alcoholic solution is used to saturate a cotton pellet which is then placed in the open cavity of a carious tooth or a tooth with a lost restoration. In contact with water or oral fluids, the sandarac precipitates, forming with the cotton a temporary filling. Such a temporary filling would, theoretically, protect exposed dental structures from air, food, or thermal changes, thereby decreasing pain originating from these stimuli. However, alcohol used as a solvent for sandarac will denature dentinal tubules and dehydrate dentin (Ref. 5). In addition, a temporary filling applied in a tooth with acute suppurative pulpitis may increase pain by blocking escape of an inflammatory exudate and gases (Refs. 5 and 6). Since the patient cannot reliably determine whether or not there is drainage from the cavity, use a self-applied temporary dental filling is not advisable. The Panel is award that beeswax, sandarac, or other ingredients which may form physical barriers in a tooth cavity may be added as inactive ingredients; however, it is considered unsafe to use these ingredients in such a manner that they do form physical barriers in a tooth cavity for reasons stated above.

The Panel is concerned that other occlusive agents which were not submitted to the Panel for review may be on the market. In this document only beeswax and sandarac are discussed as occlusive agents, but it is the intention of the Panel to recomment that all inactive ingredients which form an occlusive filling in a tooth cavity may not be included in agents for the relief of toothache intended for use in an open tooth cavity.

Because there may be a sufficient target population who could obtain temporary relief from some toothache medication, it would be helpful to have such medications remain on the market with appropriate warnings on the label.

The requirements for safety and effectiveness of agents for the relief of toothache agreed upon by the Panel are as follows:

(a) *Safety requirements for agents for the relief of toothache.* Agents for the relief of toothache should not cause sloughing or necrosis of soft tissue, should have low potential for allergenicity, should not cause a systemic effect, and should not cause irreversible damage to tissues surrounding the end of the root (periapical). In addition, combinations of ingredients including agents for the relief of toothache may be rational if it can be shown that the criteria for combination products can be met. (See part II. paragraph D. above—Principles Applicable to Combination Products.)

(b) *Effectiveness requirements for agents for the relief of toothache.* Agents for the relief of toothache must temporarily relieve the discomfort of a toothache. Although some agents for the relief of toothache may have antiseptic activity, no claims should be made for antiseptic activity because it has not been demonstrated to contribute to the effectiveness of relieving the pain of toothache. In addition, a combination of ingredients may be rational if it can be shown that each ingredient contributes to the temporary relief of discomfort as required in the Panel's combination policy. (See part II. paragraph E. above—Statements on Category III Testing Procedures.)

The Panel concludes that agents which may provide some relief of toothache are clove oil and eugenol at an equivalent concentration (85 to 87 percent) which have an anodyne effect when applied to dentin. These appear to be the best agents for the relief of toothache available and are recommended for Category I status. The Panel felt that oral mucosal analgesics are also possible agents for the relief of toothache discomfort but more data are required. Also, more data are required to test effectiveness of eugenol at lower concentrations than found in clove oil in suitable bland vehicles.

2. *Agents used for the relief of toothache applied in a poultice dosage form.* Counterirritants are irritating drugs that are applied locally to the skin or oral mucosa for the relief of pain originating from a structure other than the cite of application. Usually the counterirritant drug is applied to an area

overlying or adjacent to the deeper site which is perceived to be the origin of the painful stimulus (Ref. 7).

The Panel believes that because of their irritant nature, counterirritants for the relief of toothache should not be utilized in dosage forms intended for instillation into a tooth. Drugs classified as counterirritants, and, in general, other agents with irritant action, if instilled into a tooth cavity will injure a viable pulp. The Panel also concludes that it is irrational to apply a counterirritant to oral soft tissues which are already irritated. However, in order to relieve toothache, an irritant drug might be applied in a dental poultice to the gingiva surrounding a tooth with a painful pulpitis. Dental poultices are topical dosage forms containing medication enclosed within a porous sack. When applied to the oral mucous membrane in the presence of moisture, the dental poultice releases the medication.

The concept of usefulness of counterirritation in relief of pain of muscles, joints, and viscera from local application is widely accepted, even though such acceptance is presently based on empirical observation rather than on rigorous scientific evaluation (Refs. 3 and 7, 8, and 9). At least one counterirritant, capsicum, has had a long history of use in dental products for the relief of toothache and of pain from irritations of the gingiva. No adequate studies are avilable to prove or disprove that a counterirritant is effective in relieving oral hard or soft tissue pain.

The first response to local irritation is an increase in circulation to the site, the vasodilation being accompanied by a feeling of warmth, comfort, and sometimes pruritis (Ref. 8). The following mechanisms of pain relief by counterirritation have been postulated, and one or more of these proposed mechanisms may apply:

Sensory nerve impulses originating from irritation of the skin or mucosa are relayed in the central nervous system (CNS) to the motor nerves of blood vessels, so that increased circulation at the site of action has its counterpart in increased circulation to deeper structures innervated from the same level of the CNS (Refs. 2 and 10).

Sensory impulses arising from irritation of the skin or mucosa produce dilation of blood vessels, such as deeper arterioles, as a result of nerve reflexes (Refs. 10 and 11).

Sensory impulses arising from irritation of the skin or mucosa by the topical application of the counterirritant may alter the characteristics of the deeper sansations perceived as pain (Ref. 2).

The peripheral impulses may occupy a pathway common to both peripheral and deep impulses, resulting in a complete or partial block of those impulses arising from the deeper structures (Refs. 2 and 11).

Pain is a subjective sensation, and if a counterirritant can provide pain relief by any of the postulated mechanisms (except placebo) such pain relief should be measurable. Pain relief would probably be more easily documented if the drug were incorporated into a dosage form such as a dental ointment than if tested in a dental poultice, a dosage form which might contribute a particularly high placebo effect.

The Panel believes that there is a possibility of a dental poultice becoming accidentally lodged in the throat or in the respiratory tract if the user falls asleep with the poultice in place. The Panel, therefore, recommends that the label of products in a dental poultice dosage form carry the warning, "To avoid danger of choking do not leave a poultice in the mouth during periods of sleep." In addition, the Panel recommends the following warnings for counterirritants in a dental poultice dosage form:

"Do not instill in tooth cavity."

"Use only on healthy tissue. Do not apply to irritated oral soft tissue."

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*B. Categorization of Data*

1. *Category I conditions under which active ingredients for the relief of toothache are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

**Category I Active Ingredient**

Eugenol preparations (85 to 87 percent).

*Eugenol preparations (85 to 87 percent).* The Panel concludes that eugenol in a concentration of 85 to 87 percent in clove oil or any bland, fixed oil is safe and effective for use as an agent for the relief of toothache as specified in the dosage section below.

(1) *Safety.* Clinical use and marketing experience have confirmed that eugenol is safe for OTC use. Clove oil contains 85 to 87 percent eugenol; therefore, the Panel concludes that clove oil and eugenol essentially possess the same pharmacologic activity, and the term "eugenol" as used below indicates 85 to 87 percent eugenol in a bland, fixed oil or clove oil unless otherwise specified.

The Panel is fully aware that eugenol is sufficiently irritating to damage viable dental pulp and stresses that it should not be used in a tooth with intermittent pain (characteristic of pain caused by reversible pulp damage) (Ref. 2). The Panel concludes, however, that, with adequate labeling to indicate use only in throbbing, persistent pain (characteristic of irreversible pulp damage), eugenol is safe and effective as a toothache remedy for OTC use (Ref. 2).

In the dental literature there are reports dealing with the irritancy of eugenol preparations, especially tissue reactions to eugenol in periodontal dressings (Refs. 3, 4, and 5). In these studies none of the patients who showed irritation of the mucosa after exposure to eugenol preparations were subsequently examined by patch test for possible contact allergy, or for whether or not they had become hypersensitive to eugenol.

In one study, patients undergoing dental treatment in which eugenol-containing preparations were used, and who had reacted with swelling and redness, were patch-tested with eugenol (Ref. 6). Sixteen of 18 patients gave

clear-cut positive test reactions to eugenol. The history of these patients suggested that they had been sensitized to eugenol during dental treatment.

The amounts of eugenol used in dentistry are well below systemic toxicity levels. Aside from a few reports of hypersensitivity, the long history of use of eugenol as an anodyne attests to its safety for dental use when used on exposed dentin (Ref. 7). The use of eugenol is only recommended when there is persistent, throbbing pain. Intermittent pain may indicate that the pulp is still viable, and eugenol may compromise the pulp vitality in that case. A warning is recommended to describe when eugenol should not be used. (See part III. paragraph B.1. below—Category I Labeling.)

(2) *Effectiveness.* It is difficult to generalize about the effectiveness of a toothache preparation since the data on use of such preparations is difficult to interpret. Although data suggest that the effectiveness of self-medication is similar to that experienced with placebo drugs, eugenol's analgesic effects on dentin are recognized (Refs. 1 and 8). Well-controlled, published studies on the effectiveness of eugenol for the relief of toothache are not available. The Panel considered the opinions of acknowledged experts in endodontics who, however, did not agree with each other on the advisability of making eugenol available to the consumer as an OTC toothache remedy (Refs. 2 and 7), as well as published opinions of other experts that eugenol is a dental analgesic or has topical anesthetic effect (Refs. 1 and 9). Even though the opinions of the experts did not agree, the Panel feels that, based on all of the information evaluated by the Panel, eugenol can be generally recognized as effective as a dental analgesic and that it should be available to the consumer as an agent for the relief of toothache.

(3) *Dosage.* Adults and children 2 years of age and older: Place a cotton pledget moistened with 1 or 2 drops of 85 to 87 percent eugenol into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing active ingredients for the relief of toothache. (See part III. paragraph B.1. below—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing eugenol:

"Do not use if you are allergic to eugenol."

**References**

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**Category I Labeling**

The Panel recommends the following Category I labeling for active ingredients for the relief of toothache:

a. *Indication.* "For the temporary relief of throbbing, persistent toothache due to a cavity until a dentist can be seen."

b. *Warnings*—(1) *For all agents for the relief of toothache.* (a) "Use only in teeth with persistent, throbbing pain."

(b) "Not to be used for a period exceeding 7 days."

(c) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(d) "Do not swallow."

(e) "Do not exceed recommended dosage."

(f) "Children under 12 years of age should be supervised in the use of this product."

(g) "A dentist must be seen as soon as possible whether or not the pain is relieved."

(h) "Toothaches and open cavities indicate serious problems which need prompt attention by a dentist."

(2) *For products containing eugenol.* "Do not use if you are allergic to eugenol."

c. *Directions.* Rinse the tooth with water to remove any food particles from the cavity. Moisten a cotton pledget with 1 or 2 drops of medication and place in the cavity for approximately 1 minute. Avoid touching tissues other than the tooth cavity. Apply the dose not more than four times daily or as directed by a dentist or physician. Children 2 to 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

2. *Category II conditions under which active ingredients for the relief of toothache are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC drug products for the relief of oral discomfort effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredients**

Capsicum (for use in an open tooth cavity)
Menthol
Methyl salicylate

a. *Capsicum (for use in an open tooth cavity).* The Panel concludes that capsicum instilled into a tooth cavity is not safe for OTC use as an agent for the relief of toothache.

(1) *Safety.* Capsicum is an irritant dependent upon counterirritation for any therapeutic usefulness it may have in the relief of pain. Capsicum itself is very irritating to mucous membranes and even a minute quantity of the oleoresin will cause intense burning if it contacts the eyes or tender areas of the skin (Refs. 1 and 2). Capsicum is no longer described in "The United States Pharmacopeia" or "The National Formulary," and there are, therefore, no U.S. standards for its content of capsaicin, the active pungent constitutent. Commercial red peppers contain 0.1 to 1.0 percent of capsaicin (Ref. 3). "The British Pharmaceutical Codex" (BPC) specifies that capsicum contains about 0.5 to 0.9 percent capsaicin with the lower limit 0.5 percent; capsicum oleoresin (BPC) contains not less than 8 percent capsaicin weight/weight (w/w) (Ref. 3).

Toxicity of capsicum oleoresin is classified (with reservations) by Gosselin et al. (Ref. 1) as moderately toxic, the human lethal dose probably being 0.5 to 5 g/kg when ingested. It is very irritating to mucous membranes and if swallowed produces severe gastritis and diarrhea (Ref. 1).

In feeding studies a diet containing 0.014 percent capsaicin by weight was fed to rats for 28 and 56 days (Ref. 4). This diet produced ultrastructure

changes in duodenal absorptive cells. The amount of capsaicin ingested (approximately 1 mg/kg body weight daily) is approximately equivalent to the capsicum intake of people of rural Thailand. No histopathology studies of the effects of application of capsicum to skin or oral mucous membrane were found.

In general, irritating drugs instilled into a tooth cavity will injure a viable pulp, and OTC use of such agents by application into a tooth is unsafe.

(2) *Effectiveness.* No studies were found of the use of capsicum in dosage forms (toothache drops or toothache gum) to be instilled in the tooth cavity in order to relieve toothache pain.

(3) *Evaluation.* Use of a counterirritant for application to tissues that are irritated is irrational and unsafe. No clinical studies of the application of capsicum into a tooth cavity for relief of pain were found in the literature and none were submitted to the Panel.

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b. *Menthol.* The Panel concludes that menthol is not safe for OTC application as an agent for the relief of toothache.

(1) *Safety.* Although menthol does possess minimal anesthetic activity, if used in concentrations sufficient for anesthetic activity, it causes intense irritation with the possibility of local tissue destruction. The Panel concludes that menthol is not safe for instillation into a tooth as a local anesthetic.

Tainter, Throndson, and Moose (Ref. 1) applied a solution of 5 percent menthol in 95 percent ethanol to the oral mucous membranes of 36 humans. The menthol solution produced intense irritation when applied to oral mucosa and caused sloughs in 19 percent of the patients at a concentration of 5 percent menthol which is sufficient to produce local anesthesia. The 95 percent ethanol alone was also irritating and caused sloughs in 8 percent of the patients.

In young children, nasal drops containing menthol may cause spasm of the glottis, and cases of dangerous asphyxiation have been reported in infants following local application of menthol (Ref. 2).

The "United States Pharmacopoeia" (Ref. 3) categorizes menthol as a topical antipruritic and suggests that for external use it be applied topically to the skin as a 0.1- to 2.0-percent lotion or ointment. Concentrations of 0.1 to 2.0 percent are less than those found to have local anesthetic activity, and the "United States Pharmacopoeia" gives no indication for application of menthol to mucous membranes.

In a long-term study in experimental animals, 20 rabbits were treated with either 1-percent or 5-percent solutions of menthol in liquid petrolatum, sprayed daily to the nasal mucous membrances for 9 months (Ref. 4). Results showed that menthol produced sneezing and pain. The nose, bronchi, and lungs of all the rabbits showed some evidence of inflammatory changes, namely a purulent rhinosinobronchitis with numerous miliary abscesses and consolidation of lung tissue. The rabbits sprayed with a 5-percent menthol solution fared only slightly worse than those sprayed with the 1-percent solution. Liquid petrolatum as a control apparently also exerted a deleterious effect on the nasal mucosa of a rabbit when used for 9 months.

In general, irritating drugs instilled into a tooth cavity will injure a viable pulp; therefore, OTC use of menthol by application into a tooth is unsafe.

(2) *Effectiveness.* Nagira and Yao (Ref. 5) produced artificial toothaches in teeth of rabbits by electrical stimulation and tested the effectiveness of topical application of several agents in relieving the induced pain. They found phenol to be the best agent; clove oil, menthol, and eucalyptol were found to be weak anesthetics.

Yamashita (Ref. 6) studied the effectiveness of some local anesthetics dissolved in propylene glycol on the tympanum of guinea pigs. Dibucaine, cocaine, benzocaine, phenol, and menthol all exerted anesthetic actions and the intensities were in that order (menthol was the weakest).

In studies in humans, Adriani et al, (Ref. 7) found that a 3.5-percent menthol solution applied to the tip of the tongue produced anesthesia, with a mean latent period of 0.16 minutes and a mean duration of 1.5 minutes. This duration of action was the shortest of the 22 drugs to which local anesthetic activity was attributed.

Tainter, Throndson, and Moose (Ref. 1) applied a solution of 5 percent menthol in 95 percent ethanol to the oral mucous membranes of humans. The menthol solution produced complete anesthesia in 42 percent, partial anesthesia in 56 percent, and no anesthesia in 3 percent of 36 subjects. By comparison, 95 percent ethanol produced complete or partial anesthesia in 78 percent of the 156 persons tested, and aqueous placebo solutions proudced some degree of anesthesia in 43 percent of 576 tested. As noted above, the 5-percent menthol solution produced intense irritation when applied to oral mucosa and caused sloughs in 19 percent of the patients. They fond that a 5-percent concentration of menthol was necessary to produce local anesthesia (Ref. 1).

(3) *Evaluation.* Menthol possesses minimal local anesthetic activity, but if used in concentrations sufficient for this anesthetic activity, menthol causes intense irritation with the possibility of local tissue destruction. No claims can be made for menthol as a local anesthetic. Menthol should not, in any concentration, be instilled into a tooth cavity. Menthol may be included in preparations as an inactive ingredient (flavor) according to FDA regulations on flavors.

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c. *Methly salicylate.* The Panel concludes that methyl salicylate is not generally recognized as safe or effective for OTC application as an agent for the relief of toothache.

(1) *Safety.* Methyl salicylate causes irritation with the possibility of local tissue damage when applied to mucous

membranes (Refs. 1 and 2). In general, irritating drugs instilled into a tooth cavity will injure a viable pulp. Therefore, OTC use of methyl salicylate by application into a tooth cavity is unsafe. It is considered unsafe in conjunction with a tooth cavity even as a flavoring agent because of its irritating properties.

Because of the reputed systemic toxicity of methyl salicylate, the Panel recommends that any dentifrice or dental care agent containing this substance as a pharmaceutical aid (i.e., flavoring agent) be in conformity with all pertient regulations for its use as such.

(2) *Effectiveness.* Since there are no studies that methyl salicylate, when applied topically, provides an anesthetic effect, it apparently acts only as a counterirritant (Refs. 2 and 3).

(3) *Evaluation.* Methl salicylate is an irritant when applied topically, possible causing local tissue damage. It should not be instilled into a tooth cavity. The Panel concludes that there is no rational use of methyl salicylate as an agent to be instilled in a tooth cavity for the relief of toothache.

**References**

(1) Sollman, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 737 and 743–744, 1957.

(2) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, section II, p. 96, 1969.

(3) Traut, E. F., et al., "Topical Treatment in Rheumatic Disease," *Illinois Medical Journal*, 121:257–260, 1962.

**Category II Labeling**

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of a product are unsupported by scientific data and, in some instances, by found theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

"For quick temporary relief of pain and soreness due to minor irriation of teeth and gums." This type of toothache is not defined.

"For temporary relief of cavity toothache."

"Eases pain due to cavities fast."

"Quickly forms temporary filling."

"Fast relief from toothache due to cavities."

"Especially soothing after extractions or for minor gum boils."

"For rapid and effective relief of sore gums."

"For sore gums following tooth extractions."

"For use after tooth extraction."

"Hold in mouth as long and as frequently as necessary, then rinse." This is inconsistent with the directions for use proposed by the Panel.

"Temporary replacement for lost fillings."

"Gives quick relief that lasts for hours."

"For fast, temporary relief of minor mouth or gum soreness." The claim is too vague; it must be more specific.

"Subdues the throbbing ache of sore, swollen gums." The claim is too vague; gums may be infected or a deeper problem may exist.

The Panel considers that claims which imply a superiority in onset of action, such as "quicker," "more quickly," and "faster" are misleading.

The Panel considers the following terms to be vague and not definitive of the condition for which relief is sought: "sore spots," "anti-irritation," "comfortable adjustment," "helps comfortable adjustment," "stops pain," "soothes sore gums," "special," "unaccustomed use," "alleviates pain."

The following claims are for conditions that require advice of a dentist: "gum boils," "gum or gingival inflammation," and "abscesses."

For products containing a counterirritant: "Relieves irritation."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as noted for specific pharmacotherapeutic groups.

**Category III Active Ingredients**

Benzocaine
Benzyl alcohol (1 to 3 percent)
Butacaine sulfate
Capsicum (as a counterirritant)
Cresote
Cresol
Eugenol (1 to 84 percent)
Phenol preparations (phenol and phenolate sodium)
Thymol preparations (thymol and thymol iodide)

a. *Benzocaine.* The Panel concludes that there are insufficient data available to establish the effectiveness of 2 to 20 percent benzocaine as an OTC agent for the relief of toothache.

(1) *Safety.* The Panel has discussed the safety of benzocaine elsewhere in this document. (See part IV. paragraph B.1.a.(1) below—Safety.)

(2) *Effectiveness.* Benzocaine is classified by the Panel as an effective oral mucosal analgesic. (See part IV. paragraph B.1.a.(2) below—Effectiveness.) However, there are insufficient data to establish effectiveness of benzocaine after application into a tooth cavity, as an agent for the relief of toothache, at the 2- to 20-percent concentrations.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Place a cotton pledget moistened with 2 to 20 percent benzocaine into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing benzocaine:

"Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the effectiveness of benzocaine as an agent for the relief of toothache. Data to demonstrate effectiveness as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III, paragraph C. below—Data Required for Evaluation.)

b. *Benzyl alcohol.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of benzyl alcohol at a concentration of 1 to 3 percent for OTC use as an agent for the relief of toothache.

(1) *Safety.* There are insufficient data to establish the safety of 1 to 3 percent benzyl alcohol for use as an agent for the relief of toothache.

In general, irritating drugs instilled into a tooth cavity will injure a viable pulp, and OTC use of such agents by application into a tooth is unsafe. An additional problem is that application of benzyl alcohol into a tooth cavity may increase permeability of the dentin. Application of benzyl alcohol into the tooth may, therefore, increase any adverse effects of other drugs applied concomitantly (Ref. 1). Benzyl alcohol in 100 percent concentration is irritating to tissue; injected subcutaneously or intramuscularly, the drug produces local necrosis (Refs. 2, 3, and 4).

When injected in the area of branches of the facial nerve in cats, 10 percent benzyl alcohol in almond oil produced

prolonged motor nerve block, and it caused degeneration of nerve fibers in the injected area (Ref. 5). Tested in the same way, 5 percent benzyl alcohol in almond oil produced only transient weakness of the appropriate muscles, but even this lower concentration caused degeneration of a significant number of nerve fibers. Almond oil itself has no observable effect on the nerve fibers.

Aqueous solutions in concentrations from 1 to 3 percent of benzyl alcohol may produce variable degrees of irritation to soft tissues. Aqueous preparations containing greater than 3 percent benzyl alcohol are likely to contain undissolved benzyl alcohol. The studies cited above show that undissolved benzyl alcohol is a potent irritant. Therefore, preparations greater than 3 percent may be unsafe for instillation into a tooth cavity for the relief of toothache or for application to oral soft tissues.

Because animal studies suggest that ingestion of benzyl alcohol at a rate of 1 mL/kg may be fatal (Ref. 1), and since package sizes that will provide more than 30 mL of a 2-percent solution of 60 mL of a 1-percent solution are unnecessary and may be a potential risk for accidental ingestion by young children, the Panel recommends that package size be limited to that containing a total of 0.6 mL of benzyl alcohol.

(2) *Effectiveness.* The Panel has discussed the effectiveness of benzyl alcohol elsehwere in this document. (See part IV. paragraph B.3.a.(2) below—Effectiveness.) Benzyl alcohol does have local anesthetic activity, but studies of effectivness by application into a tooth cavity for the relief of toothache are not available.

Since benzyl alcohol solutions stored in soft glass containers have been shown to increase in pH and drecrease in anesthetic ativity, the Panel believes there may be stability problems with blezyl alcohol solutions in some dosage forms or in some types of packaging. Therefore, the stability of benzyl alcohol in the particular dosage form and packaging intended for marketing should be established (Ref. 6).

(3) *Proposed dosage,* Adults and children 2 years of age and older: Place a cotton pledget moistened with 1- to 3-percent benzyl alcohol into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache, (See part III. paragraph B.1. above—Category I Labeling).

In addition, products containing benzyl alcohol should contain no more than a total of 0.6 mL (30 mL of a 2-percent solution or 60 mL of a 1-percent solution) of benzyl alcohol in a container capable of maintaining stability of the product.

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the safety and effectiveness of 1 to 3 benzyl alcohol as an agent for the relief of toothache. Data to demonstrate safety and effectiveness as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

Benzyl alcohol does possess local anesthetic activity, but the concentrations (in aqueous and nonaqueous solvents) needed to provide relief of pain arising from the tooth pulp have not been established. Benzyl alcohol at a concentration of 100 percent is a potent irritant, and the maximal safe concentrations (in aqueous and nonaqueous solvents) of solutions for application to oral mucosa have not been established. Since only 1 g of benzyl alcohol is soluble in about 25 to 30 mL of water, aqueous preparations containing more than 3 to 4 percent benzyl alcohol may produce irritation as a result of some undissolved benzyl alcohol.

**References**

(1) Macht, D. I., "A Pharmacological and Therapeutic Study of Benzyl Alcohol as a Local Anesthetic," *Journal of Pharmacology and Experimental Therapeutics,* 11:263–279, 1918.

(2) Macht, D. I., "Further Experiences, Experimental and Clinical, with Benzyl Benzoate and Benzyl Alcohol," *Journal of Pharmacology Proceedings,* 13:509–511, 1919.

(3) Gruber, C. M., "The Pharmacology of Benzyl Alcohol and Its Esters: I. The Effect of Benzyl Alcohol, Benzyl Acetate and Benzyl Benzoate when Given by Mouth upon the Blood Pressure, Pulse and Alimentary Canal," *Journal of Laboratory and Clinical Medicine,* 9:15–33, 1923.

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(5) Duncan, D., and W. H. Jarvis, "A Comparison of the Actions on Nerve Fibers of Certain Anesthetic Mixtures and Substances in Oil," *Anesthesiology,* 4:465–474, 1943.

(6) Bender, I. B., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 14th meeting, October 16, 1974. (See Appendix II to the minutes of the 15th meeting, December 4–5, 1974.)

c. *Butacaine sulfate.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 4 percent butacaine sulfate as an agent for the relief of toothache.

(1) *Safety.* Butacaine sulfate is classified by the Panel as a safe oral mucosal analgesic. (See part IV, paragraph B.1.c. (1) below—Safety.) However, the Panel concludes that there are insufficient data to establish the safety of 4 percent butacaine sulfate as an agent for the relief of toothache.

(2) *Effectiveness.* Butacaine sulfate is classified by the Panel as an effective oral mucosal analgesic. (See part IV. paragraph B.1.c. (2) below—Effectiveness.) However, there are insufficient data to establish effectiveness of 4 percent butacaine sulfate after application into a tooth cavity as an agent for the relief of toothache.

(3) *Proposed dosage.* Adults and children 12 years of age and older: Place a cotton pledget moistened with 4 percent butacaine sulfate into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warnings for products containing butacaine sulfate:

(a) "Do not use in children under 12 years of age unless recommended by a dentist or physician."

(b) "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 4 percent butacaine sulfate as an agent for the relief of toothache. Data to demonstrate the safety and effectiveness of butacaine sulfate as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

(d) *Capsicum (as a counterirritant.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of capsicum equivalent to 0.01 to 0.02 percent of capsaicin for OTC use as an agent for the relief of toothache as a counterirritant on intact (normal) oral mucosa as specified in the proposed dosage section discussed below. Capsicum is safe for application to normal oral mucous membranes, but is considered unsafe for application into a tooth cavity or for use on irritated oral

mucosa. (See part III. paragraph B.2.a. above—Capsicum.)

(1) *Safety.* Clinical use and marketing experience have confirmed that capsicum equivalent to 0.02 percent of capsaicin is safe for OTC use on normal oral mucosa.

As used in drug products intended for application to skin or mucous membrane, the desired pharmacologic effect of dilutions of capsicum and capsicum oleoresin is a mild local irritation. Safety evaluations are related to estimation of the degree of local irritation produced by acute use of a counterirritant in a suitable dosage form and chronic irritation due to prolonged application which could theoretically have some adverse effects, but long-term use would be excluded by proper labeling. Package size should be limited to a maximum amount for eight applications so as to discourage prolonged use.

Two evaluations of dental poultices containing capsicum contribute some limited information on irritant effects, or lack thereof, of capsicum or oral mucosa. In 1936 a dental poultice stated to contain 2.3 percent capsicum, and 6 other ingredients (including aconite, which is an irritant) was evaluated by the Council on Dental Therapeutics of the American Dental Association (Ref. 1). Tests by a pharmacologist in which three subjects applied the test poultice to the buccal cavity on one side and a poultice composed of hops on the other side showed no burning or erythema at the site of application on either side. The capsicum poultice produced very mild burning on the tongue.

The poultice was reformulated and again submitted to the Council (Ref. 2). The revised formula contained 2.3 percent capsicum with 3 percent benzocaine and 4 ingredients stated by the reference to be inactive. The report states, "Laboratory and clinical studies indicate that this product will produce no harmful local effects." The report summarizes four clinical studies, only one of which mentions tissue irritation or lack thereof. In this study, reddening of the oral mucosa was evaluated after 1-hour contact with the poultice and with a control poultice. In 30 subjects the medicated poultice produced hyperemia to the same or less degree than the control poultice; in 20 subjects there was more hyperemia from the medicated poultice than from the control poultice. It must be noted, however, that the literature is conflicting in regard to whether or not capsicum is a rubefacient, and hyperemia may not be a valid measure of irritant effect (Refs. 3, 4, and 5). In addition, a local anesthetic may inhibit the local vasodilation response to a rubefacient drug (Ref. 6). (See part III. paragraph B.2.a. (1) above—Safety.)

(2) *Effectiveness.* As an active ingredient of dental poultices, capsicum is claimed to provide relief of toothache (as a counterirritant) when the poultice is applied to the gum.

A published Council on Dental Therapeutics report (Ref. 2) on the effectiveness of a capsicum-containing poultice includes the only four clincial studies that could be found. The poultice contained 2.3 percent capsicum, 3 percent benzocaine, and 4 other ingredients, including hops, labeled as inactive ingredients. In the first study, which was sponsored by the manufacturer, participating dentists alternately gave the test poultice or a hops poultice to patients suffering mild pain. The patients were asked to report (on a card) the rapidity and degree of pain relief afforded by the poultices. The company reported that the medicated poultice showed measurable superiority over the placebo, but the company also noted that the results of this first study were not particularly conclusive. The Council itself conducted a similar study, except that efforts were made to prevent the dentist and the patient from identifying which poultice was the active one. Results indicated no particular superiority of the capsicum-benzocaine poultice over the placebo. There was a very high placebo response. In a third study, a placebo "pill" was compared with the test poultice. The results were more favorable for the poultice than for the pill, but of course the control drug was an inadequate control. The fourth study was a double-blind, controlled study conducted by the Council's referee. The subjects were dental students. The medicated poultice was placed on one side of the maxilla in the bicuspid area, and the placebo was placed on the other side. After 1 hour of application the effects were evaluated, including taste (burning and bitter), hyperemia of the tissues, and tissue sensitivity. Only in taste was there a statistically significant difference between the placebo and test poultices. This fourth study did not attempt to evaluate relief of clinical pain. Measuring "tissue sensitivity" would evaluate the effects of the benzocaine component, but not the effects of capsicum.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Apply 0.01 to 0.02 percent capsicum in a dental poultice dosage form.

(4) *Labeling.* The Panel recommends the Category I labeling for agents for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warnings for products containing capsicum:

(a) "Do not install in tooth cavity."

(b) "Do not apply to irritated oral soft tissue. Use only on healthy tissue."

(c) "To avoid danger of choking, do not leave a poultice in the mouth during periods of sleep."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the effectiveness of 0.01 to 0.02 percent capsicum as an agent for the relief of toothache (counterirritant). Data to demonstrate effectiveness as an agent for the relief of toothache as a counterirritant will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

Although capsicum appears to be a safe drug when it is used occasionally in low concentrations for topical application to oral mucous membranes, there are presently no data to indicate what concentration of capsicum is needed for effectiveness when applied in this way as a counterirritant.

If effective, capsicum will only relieve pain symptoms and may, therefore, disguise the true disease process. For this reason and because chronic irritation is unsafe, products containing capsicum should be labeled to indicate only temporary use.

Effectiveness should be established by two well-controlled clinical studies in which a capsicum dosage form affords significantly ($P \leq 0.05$) more pain relief than the appropriate placebo. Accepted indices of analgesic effectiveness, such as pain intensity differences (PID), total pain relief (TOTPAR), or numbers of patients with pain reduction greater than 50 percent, could be used to evaluate effectiveness of capsicum in relieving clinical pain originating from oral tissues. Two years should be allowed for such studies.

**References**

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(4) Osol, A., et al., "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., J. B. Lippincott Co., Philadelphia, pp. 237–238, 1967.

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(6) Fulton, G. P., E. M. Farber, and A. P. Moreci, "The Mechanism of Action of Rubefacients," *Journal of Investigative Dermatology*, 33:317–325, 1959.

e. *Creosote.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 0.25 to 1.5 percent creosote as an agent for the relief of toothache.

(1) *Safety.* Creosote, beechwod creosote, is obtained by the distillation of wood tar and is composed of a large number of phenolic compounds, the greater quantities of which are guaiacol (2-methoxyphenol) and creosol or methylguaiacol (2-methoxy,4-methylphenol) (Ref. 1). These phenols have toxicities similar to, but less than, that of phenol (Ref. 2). Like phenol, creosote and guaiacol are absorbed through the skin and mucous membranes (Refs. 2, 3, and 4). Phenols are protoplasmic poisons (Ref. 5). Although stated to be somewhat less toxic than phenols, creosote and its two major constitutents, creosol and guaiacol, are irritant corrosive fluids capable of damaging tooth pulp and destroying nerves (Refs. 2 and 6). As with phenol, the maximum safe concentration of creosote for application to an open tooth cavity has not been established. The depth of the tooth cavity, and therefore its proximity to the pulp, is a major factor in the safety of placing any kind of medication into the tooth, since these medications may cause pulpal irritation, resulting in irreversible damage.

(2) *Effectiveness.* Creosote is similar to phenol in that when it is applied locally it paralyzes sensory nerves and is anesthetic as well as being irritating and germicidal (Ref. 6). Application of a droplet of full-strenth creosote to the cavity of a carious tooth usually relieves toothache temporarily (Ref. 3). However, no data were presented or found in the literature on effectiveness of solutions of creosote in the treatment of toothache, and irritant properties of creosote preclude its OTC use in full-strength.

(3) *Proposed dosage.* Adults and children 6 years of age and older: Place a cotton pledget moistened with 0.25 to 1.5 percent creosote into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache. (See Part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing creosote:

"Do not use in children under 6 years of age unless recommended by a dentist or physician."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 0.25 to 1.5 percent creosote in the tooth cavity for the relief of toothache. Data to demonstrate safety and effectiveness of creosote as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—data Required for Evaluation.) These studies should be completed in a 30-month period.

**References**

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 355, 1973.

(2) Gosselin, R. E., *et al.*, "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, Section II, p. 126, 1976.

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(6) Osol, A., et al., "The Dispensatory of the United States," 24th Ed., J. B. Lippincott Co., Philadelphia, p. 338, 1947.

f. *Cresol.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 0.25 to 1.0 percent cresol as an OTC agent for the relief of toothache.

(1) *Safety.* Cresol, a mixture of 2-, 3-, 4-methylphenols is obtained by fractional distillation of coal tar or petroleum (Refs. 1 and 2). Cresol is a protoplasmic poison resembling phenol in its effects although it may be slightly more corrosive than phenol, and its systemic effects may be slightly milder because of slower absorption (Refs. 3 and 4). In an in vitro test, 0.25 percent cresol, 0.54 percent phenol, 0.3 percent *m*-cresol, and 1.2 percent benzyl alcohol produced total hemolysis of erythrocytes (Ref. 5). In a study of carcinogenic activity of phenol and related compounds on mouse skin, each of the three cresols was reported to have the same order of "promoting" activity as phenol (Ref. 6).

On the skin, cresol produces erythema, burning, and numbness (Ref. 2). If ingested, cresol causes a severe burning sensation in the mouth and upper abdomen, dysphagia (difficulty in swallowing), vomiting, and diarrhea (Ref. 2). Chronic poisoning (by ingestion or by percutaneous absorption) may produce widely varied reactions such as gastrointestinal disturbances, central nervous system dysfunctions, skin eruptions, jaundice, oliguria, and uremia (Ref. 7). At least one death has been reported from topical application of cresol to a large area of the body surface of a child (Ref. 8). Irritation of periapical tissues may occur if cresol is used in root canal therapy (Ref. 1).

(2) *Effectiveness.* Early studies in experimental animals and man suggest that cresol solutions have some local anesthetic activity (Refs. 9 through 12). Gurney (Ref. 13) reports that cresols have been used as mild pulpal analgesics and that when applied under proper conditions they exhibit a demonstrable analgesia. He notes that the analgesia may be easily seen with application of cresol to irritated pulps of primary teeth but that analgesia is very difficult to demonstrate with permanent teeth. Gurney's paper did not include clinical studies.

The Panel conducted a thorough search of the scientific literature for clinical studies of cresol as a local anesthetic for use on soft oral tissue or for the relief of toothache. Such studies were not found. One submission included one unpublished clinical study of the obtundent qualities of a product containing cresol and boric acid (Ref. 14). This clinical study apparently included more than 120 patients, but it was uncontrolled, not well-documented, and evaluations were subjective.

(3) *Proposed dosage.* Adults and children 6 years of age and older: Place a cotton pledget moistened with 0.25 to 1.0 percent cresol in aqueous solution into the tooth cavity for approximately 1 minute. The total amount to be applied in a 24-hour period should not exceed 400 mg for adults or 200 mg for children 6 to 12 years of age.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing cresol:

"Do not use in children under 6 years of age unless recommended by a dentist or physician."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 0.25 to 1.0 percent cresol in the tooth cavity for the relief of toothache. Data to demonstrate safety and effectiveness of

cresol as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 209, 1977.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 355, 1973.

(3) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 63, 1977.

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(9) Ikebe, S., "Experimental Study on Surface Anesthesia of the Outer Ear Passage in Guinea Pigs," (abstract), *Chemical Abstracts,* 29:2599, 1935.

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(11) Kasuga, E., "Percutaneous Anesthesia," (abstract), *Chemical Abstracts,* 34:7428, 1940.

(12) Sata, S., "Physicochemical Studies on the Anesthetic Poetncy of Phenolic Compounds: II. Anesthetic Potency on Sciatic Nerve of Frog," (abstract), *Chemical Abstracts,* 64:20415, 1966.

(13) Gurney, F. F., "Substituted Phenols: Part Two—Cresols, Cresylacetate, Formocresol," *Dental Digest,* 78:314–316, 1972.

(14) OTC Volume 080013.

g. *Eugenol (1 to 84 percent).* The Panel concludes that 1 to 84 percent eugenol is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC agent for the relief of toothache.

(1) *Safety.* The Panel has discussed the safety of eugenol elsewhere in this document. (See part III. paragraph B.1.(1) above—Safety.)

(2) *Effectivenes.* The Panel concludes that eugenol in concentrations of 1 to 84 percent may be effective as an agent for the relief of toothache since it is recognized as effective at a concentration of 85 to 87 percent. (See part III. paragraph B.1.(2) above—Effectiveness.) However, there are insufficient data to establish the effectiveness of eugenol in lower concentrations (Refs. 1 and 2). The Panel, therefore, recommends that studies be conducted within this dosage range.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Place a cotton pledget moistened with 1 to 84 percent eugenol into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing eugenol:

"Do not use if you are allergic to eugenol."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the effectiveness of 1 to 84 percent eugenol in the tooth cavity for the relief of toothache. Data to demonstrate the effectiveness of 1 to 84 percent eugenol as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

**References**

(1) OTC Volume 080003.

(2) OTC Volume 080081.

h. *Phenol.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of phenol in concentrations up to 1.5 percent for OTC use as an agent for the relief of toothache as specified in the proposed dosage section below.

(1) *Safety.* The Panel concludes that phenol in concentrations up to 1.5 percent in aqueous solution is safe for application to oral mucous membranes, but the maximum safe concentration for application to an open tooth cavity has not been established. The depth of the tooth cavity and therefore its proximity to the pulp is a major factor in the safety of placing any kind of medication into the tooth because these medications may cause pulpal irritation resulting in irreversible damage.

The opinions of two acknowledged research experts in endodontics cite phenol's capacity to damage odontoblasts by increasing the permeability of dentinal tubules (Refs. 1 and 2). They further state that phenol, as a protoplasmic poison, may stop pain, but its potential to produce pulp damage warrants its elimination from toothache preparations. Nevertheless, the Panel had no convincing evidence that phenol in concentrations up to 1.5 percent was unsafe and therefore placed it in Category III. (See part IV. paragraph B.1.c.(1) below—Safety.)

(2) *Effectiveness.* The local anesthetic activity of low concentrations of phenol is due to its ability to block nerve conduction, but this action is limited. High concentrations demyelinate or otherwise destroy many types of nerve endings (Refs. 3 and 4).

The effectiveness of phenol as an agent for the relief of toothache has never been demonstrated. Originally, phenol was used in dentistry for so-called "cavity sterilization"; however, because high concentrations of phenol have been shown to do more harm than good by increasing the permeability of dentin, its use is no longer advocated (Refs. 1 and 2). (See part IV. paragraph B.1.c.(2) below—Effectiveness.)

(3) *Proposed dosage.* Adults and children 2 years of age and older: Place a cotton pledget moistened with 1.5 percent phenol in aqueous solution into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing active ingredients for the relief ot toothache. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of phenol as an agent for the relief of toothache. Data to demonstrate safety and effectiveness of phenol as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

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i. *Thymol preparations (thymol and thymol iodide).* The Panel concludes that thymol preparations in concentrations up to 20 percent are safe

but that there are insufficient data available to permit final classification of their effectiveness for use as OTC agents for the relief of toothache as specified in the proposed dosage section below.

(1) *Safety.* The acute toxicity of thymol in a solution of propylene glycol was determined by oral administration to experimental animals (Ref. 1). Groups of 10 young adult Osborne-Mendel rats, evenly divided by sex, were fasted for approximately 18 hours and given the test material. The $LD_{50}$ was 0.98 g/kg with a death time ranging from 4 hours to 5 days. The toxic signs with high doses consisted of depression, ataxia (failure of muscle coordination), and coma.

The minimum oral lethal dose of thymol has been reported to be 800 mg/kg in the mouse, 750 to 1,000 mg/kg in the rabbit, and 250 mg/kg in the cat (Ref. 2).

Thymol is considered to be less toxic than phenol. In humans fats and alcohol increase absorption and aggravate the toxic symptoms (Ref. 3). Thymol is completely absorbed from the intestine. It is excreted in the urine as the sulfate and glucuronide together with some thymol-quinone. About half of a dose is destroyed in the body. Thymol is an irritant to the kidneys (Ref. 3).

There are no apparent studies on thymol iodide; however, when thymol iodide was fed to rats for 5 weeks in a study designed to demonstrate iodide availability, there was considerable uptake of iodide by the thyroid (Ref. 4).

Boutwell and Bosch (Ref. 5) studied over 50 compounds related to phenol for their ability to promote the development of skin following a single initiating dose of dimethylbenzanthracene. One of the compounds tested (2-isopropyl-4-methylphenol) is closely related to thymol. When dissolved in 16 percent benzene and applied weekly for 12 weeks to mice, 19 percent developed skin tumors and 6 percent (1 and 16 mice) developed a carcinoma.

"The United States Dispensatory" (Ref. 6) states that thymol can cause nausea, vomiting, albuminuria, headache, tinnitus, dizziness, muscular weakness, a thready pulse, slow respiration, and a full in body temperature. It further states that the heart is depressed by "therapeutic" doses. Thymol used systemically in the treatment of mycosis has been given as divided oral doses consisting of 1 to 2 g daily being administered in courses of 2 of each 3 days. It has also been used as an intestinal antiseptic, in doses up to 120 mg.

Gleason et al. (Ref. 7) state that the toxicity of thymol is believed to lie on the borderline between toxicity classes 3 and 4 (moderately toxic and very toxic).

Thymol is less toxic than phenol, and larger doses may be taken (Ref. 3). It generally irritates tissues and given orally irritates the gastric mucosa. Rashes from thymol are not uncommon (Ref. 3). It was formerly used for the treatment of hookworm infestations, but it had to be used in such large doses that there was danger of serious, even fatal, poisoning. Oral doses stimulate peristalsis and may cause diarrheal stood (Ref. 6).

Thymol should not be given by mouth to persons with gastrointestinal disorders or impaired kidney function. It should be given with care to patients with heart disease (Ref. 3). However, the amounts used topically in the oral cavity are insufficient to cause problems for these individuals.

(2) *Effectiveness.* Thymol is used chiefly as a deodorant in antiseptic mouthwashes and gargles. Mixed with phenol and camphor, thymol is used in dentistry to prepare cavities before filling, and mixed with zinc oxide it forms a protective cap for the dentine (Ref. 3).

There are reports of use of thymol or thymol iodide in products for the relief of toothache, but there are insufficient data to establish effectiveness (Refs. 1 through 7). Since eugenol and thymol are chemically similar, the possibility of effectiveness as an agent for the relief of toothache is suggested and has frequently, in fact, been associated with professional use for this purpose (Ref. 3).

(3) *Proposed dosage.* adults and children 2 years of age and older: Place a cotton pledget moistened with a maximum of 20 percent thymol or thymol iodide in the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there is insufficient information to establish the effectiveness of thymol preparations as agents for the relief of toothache. Data to demonstrate effectiveness as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

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*Category III Labeling*

None.

*C. Data Required for Evaluation*

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing agents for the relief of toothache*—a. *General principles.* As far as the Panel could determine, no acceptable studies had been published which prove effectiveness of an agent for the relief of toothache. The recommendation of eugenol (85 to 87 percent) in oil of cloves for Category I was made on the basis of a long history of use by dental practitioners. The Panel recommends that Category III agents for the relief of toothache be tested using the following protocol. Also, the Panel would like to encourage industry to study eugenol and oil of cloves using the same protocol in order to determine the performance of such standards. Such data would be useful in either verifying the Panel's conclusions or for future amendment of the monograph.

b. *Selection of patients.* Patients are screened when they enter the program to determine whether they have severe, throbbing, and persistent toothache which is described as intolerable. Subjects should be restricted to adults 20 to 50 years of age not taking central nervous system medications or having physical illness.

c. *Study method.* Three investigators at separate institutions, preferably academic institutions, should perform these studies. The general plan should be a sequential analysis as described in

several publications (Refs. 1, 2, and 3). The medication and placebo should be coded with random numbers and supplied in pairs.

Patient A receives one of the pair of medications. The tooth cavity is gently rinsed with warm water and the medication is placed in the cavity on a piece of cotton. The cotton is removed after 5 minutes. In the case where the agent for the relief of toothache is a gel, the gel is placed directly in the tooth cavity without cotton and allowed to leach out. The investigator then asks the patient to determine whether the pain is now tolerable. If the pain is still intolerable, no relief is noted for patient A and the dentist performs his or her normal procedure on the tooth according to diagnosis. To determine the duration of tolerable pain the same inquiry is conducted every 10 minutes for 90 minutes or until the subject says the pain has become intolerable again. At that time, the dentist performs his or her normal procedure on the tooth according to diagnosis.

Patient B receives the second medication of the pair, and the same procedure is followed. The code is broken, and a point is plotted on the sequential chart as follows:

(1) The active vs. placebo no point plotted: no relief obtained with either agent, or both agents provided relief but relief did not last at least 20 minutes more for one agent than for the orther.

(2) Active better than placebo: pain becomes tolerable in the active-agent subject and remains so for 20 minutes more than for the placebo subject.

(3) Placebo better than active: Pain becomes tolerable in the placebo subject and remains so for 20 minutes more than in the active-agent subject.

d. *Interpretation of data.* Pairs of patients are repeated whenever they become available until statistical significance (p less 0.05) is reached on the sequential analysis chart. No attempt is made to pair patients other than on the basis of time of arrival. Blinding of the investigator and the subject may be difficult with aromatic substances such as eugenol and thymol. It is recommended that a third bottle be supplied with each pair of test agents. This bottle should contain 85 to 87 percent eugenol or oil of cloves. It should be opened first before opening any coded medication. Just before the test substance is applied to the tooth a small amount of eugenol is placed on the tongue. This procedure may, to some degree, mask the effect of taste and odor. In addition, placebo and test substance should resemble each other in color and viscosity.

Also, the safety of benzyl alcohol, butacaine, creosote, cresol, and phenol as agents for the relief of toothache should be demonstrated by well-designed studies in the tooth cavities of humans under conditions of proposed use.

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2. *General principles in the design of an experimental protocol for testing counterirritants as agents for the relief of toothache.* Currently there are no generally accepted protocols for testing the effectiveness of counterirritant ingredients. The Panel recommends that the industry and FDA consider and develop mutually acceptable methodology.

The only counterirritants considered by the Panel were intended for application to the gum. Factors involved in the testing of agents for the relief of toothache, as discussed above, would be applicable as well to testing counterirritants and would provide a useful basis for comparison. (See part III. paragraph C.1. above—General principles in the design of an experimental protocol for testing agents for the relief of toothache.) This approach has not been previously used in testing counterirritants, but is pertinent to such ingredients which may claim to relieve toothache by the application of a poultice. (See part III. paragraph B.3.d. above—Capsicum.)

## IV. Oral Mucosal Analgesics (Topical Anesthetics)

### *A. General Discussion*

Oral mucosal analgesics are surface or topical anesthetics, and they are used as dental care agents by surface application to provide temporary relief of oral discomfort. Some injectable local anesthetics have surface anesthetic properties when applied topically in ointment, gel, or other topical dosage forms. Included in this category are lidocaine and butyl-derivatives of procaine, such as tetracaine and butacaine (Ref. 1). Benzocaine (ethylaminobenzoate) is very commonly used as a surface anesthetic; slow absorption makes it safe for use on wounds and mucous membranes (Ref. 2). Benzocaine is chemically related to procaine, but because of its lack of water solubility it is not useful as an injectable local anesthetic (Ref. 1).

The most commonly used surface anesthetics for OTC dental use are benzocaine and butacaine; for dental office use, lidocaine and tetracaine are the most commonly used (Ref. 3). Another drug, dyclonine is chemically dissimilar to commonly used surface anesthetics and may be used in dental offices for patients allergic to procaine, benzocaine, or chemically similar drugs (Ref. 1). In addition, combinations of surface anesthetics are often used in dental offices.

Various aromatic principles and alcohols also have modest to intense surface anesthetic effects. Tainter (Ref. 4) found that phenol, benzyl alcohol, menthol, and chlorobutanol have topical anesthetic activity. However, he claimed that phenol (used at 5 percent) was too caustic to be useful, while chlorobutanol at 10 percent and menthol at 5 or 10 percent were irritating. Studies by Adriani et al. (Ref. 5) indicated that classical injectable local anesthetics that are highly toxic (tetracaine, cocaine, dibucaine, and butacaine) were also highly effective surface anesthetics, while aromatic compounds (benzyl alcohol and menthol) were not nearly as effective.

1. *Adverse effects.* Adverse effects from surface anesthetics are due to overdosage, local irritation, or allergy.

a. *Overdosage.* Most anesthetic bases are rapidly absorbed when applied on the mucosal tissues (Ref. 6). Therefore, the maximum permissible dose (MPD) by intravenous injection should not be exceeded when applying the drug to the oral mucosa. Tetracaine and dibucaine have low MPD's because of high toxicity on intravenous administration (Ref. 4). These drugs are absorbed rapidly from the oral mucosa. When used as an agent to be applied topically to the oral mucosa, the dosage which is absorbed may exceed a safe dose and may cause systemic toxicity including seizures (Ref. 5). Their use should be closely supervised by a dentist.

Benzocaine appears to be an ideal surface anesthetic because, even when applied at high concentrations, overdosage is not likely to occur. Furthermore, it does not irritate the tissues at concentrations used in OTC products. Butacaine, although frequently used in dental ointments, has toxicity about equal to tetracaine. This toxicity level caused the Panel some concern, but based on safety studies provided during Panel deliberations, a long history of safe use, and a lack of adverse reaction reports, the Panel recommends butacaine for Category I classification (Refs. 1, 2, and 3).

b. *Local irritation.* As noted above, local irritation from surface application occurs only with a higher concentration of aromatic compounds or alcohols. The Panel considered local irritation as a a limiting factor in determining maximum safe concentrations of these agents.

c. *Allergy.* Although allergy to local anesthetics is considered rare, it does occur, especially with drugs related chemically to procaine. Benzocaine and butacaine are both in this category. Patients who are allergic to "caine" anesthetics should be warned on the package labeling, "Do not use this product if you are allergic to (name of local anesthetics) or other 'caine' anesthetics." These patients should use topical anesthetics only under the supervision of a dentist or physician. Since allergies to local anesthetics are quite rare, the target population for a new nonallergenic anesthetic would be extremely small; thus, there may not be an incentive to develop an OTC anesthetic which has no cross-reactivity with currently used local anesthetics.

Dental indications for use of topical anesthetics for the relief of oral discomfort include temporary relief of pain due to minor irritation or injury of soft tissues of the mouth, temporary relief of pain due to minor dental procedures, temporary relief of pain due to minor irritation of soft tissues caused by dentures or orthodontic appliances, temporary relief of pain due to canker sores when the condition has been previously diagnosed by a dentist or physician, and temporary relief of sore gums of infants and children due to teething.

2. *Carcinogenicity of phenol and phenolic compounds.* The Panel was concerned with reports of the carcinogenic and cocarcinogenic potential of phenol and phenolic substances, especially the studies of Boutwell and his coworkers and other groups (Refs. 7 through 13). Therefore, in addition to thorough study by the Panel, two experts were invited to make presentations to the Panel (Refs. 14 and 15).

These presentations were especially helpful, since they presented current views of earlier studies. The key point was that the cocarcinogenic effect of phenolic compounds is reversible and that low concentrations by themselves are not carcinogenic. Thus, if concentrations such as those recommended for mouth rinses or other OTC preparations are sufficiently low and the period of their use is restricted, there is no evidence that such use induces oral carcinoma. The Panel accepted 1.5 percent phenol in aqueous solution or in 20 percent ethyl alcohol as a dental rinse or in 70 percent ethyl alcohol for direct application to gums as the maximum generally recognized as safe (GRAS) concentration with a limit of 7 days use for any course of therapy, unless treatment is under the supervision of a dentist or physician. (See part IV. paragraph B.1.c. below—Phenol.) Under these conditions phenol and similar compounds are considered GRAS.

Cresol, a phenolic compound, is recommended for Category III requiring effectiveness studies with the safe concentration ranging from 0.25 to 1 percent. The same time limitation of 7 days is recommended for cresol and phenol labeling. (See part IV. paragraph B.3.b. below—Cresol.)

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*B. Categorization of Data*

1. *Category I conditions under which oral mucosal analgesic active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

**Category I Active Ingredients.**

Benzocaine
Butacaine sulfate
Phenol preparations (phenol and phenolate sodium)

a. *Benzocaine.* The Panel concludes that 5 to 20 percent benzocaine base in appropriate vehicles is safe and effective for OTC use as an oral mucosal analgesic for the relief of oral discomfort as specified in the dosage section discussed below. Appropriate vehicles are polyethylene glycol or propylene glycol water-soluble bases, ointment bases, ethyl alcohol up to 70 percent (maximum dosage 1.0 mL), and denture adhesive powders or creams.

The local anesthetic benzocaine (ethyl aminobenzoate) is the ethyl ester of para-aminobenzoic acid (Refs. 1 through 4). It has also been named anesthesin, orthesin, and parathesin. It occurs as an odorless, white, crystalline solid, which is very slightly soluble in water (1:2,500), soluble in alcohol (1:5), and soluble in almond and olive oils (1:30 to 1:50) (Ref. 2). Propylene glycol and polyethylene glycol may be used as water-miscible solvents for benzocaine.

(1) *Safety.* Clinical use and marketing experience have confirmed that benzocaine is safe for OTC use. It is one of the more widely used and safest topical anesthetics found in OTC preparations. It has been widely used since 1903. When applied, benzocaine is absorbed so slowly from oral tissues and wounds that reactions due to systemic toxic effects are virtually unknown (Refs. 1 and 5). The seizures and cardiac depressant characteristics of overdose of "caine" type drugs do not occur with benzocaine, and reports of such reactions with the use of benzocaine are nonexistent (Ref. 6).

Safety in part is due to hydrolysis of the drug by pseudocholinesterases in blood plasma which detoxifies esters of aminobenzoic acid.

Benzocaine has been administered orally to relieve stomach pain without any resulting toxic effects. The Panel is unaware of any fatalities due to oral ingestion of benzocaine and the lethal dose in man is not known.

Lethal doses have been determined in animals when benzocaine has been administered by various routes. When administered to rabbits, the $LD_{50}$ for benzocaine was 146 mg/kg by the intratracheal route and 104 mg/kg intranasally (Ref. 7). In this study, a comparison with other commonly used anesthetics indicated that benzocaine is the safest.

Benzocaine therapy is not absolutely without adverse effects. Benzocaine in high doses may cause methemoglobinemia, because it can interfere with the reconversion of methemoglobin to hemoglobin (Refs. 1 and 5).

Cyanosis appears when 2 g or more of total adult hemoglobin have been converted to methemoglobin (the latter is incapable of carrying oxygen). Most reported systemic reactions were in infants under 6 months of age who were treated with benzocaine suppositories (Refs. 8 through 11). Infants under 4 months may be more susceptible than older infants, children, or adults because of their relative deficiency of DPNH-dependent methemoglobin reductase, an enzyme which protects against methemoglobin-inducing foreign compounds (Ref. 11). Some infants under 4 months of age may not have developed sufficient quantities of the reductase to prevent development of methemoglobinemia upon exposure to benzocaine.

A congenital deficiency of the enzyme in older children or in adults is rare. There are three cases reported in the literature of adults who developed methemoglobinemia within 3 hours of ingestion of benzocaine in 162.5-mg to 325-mg doses (Refs. 11 and 12). These reactions were of a mild nature.

When caused by the amounts absorbed from a single application of benzocaine, methemoglobinemia is not life threatening since the oxygen capacity is not significantly decreased. It is extremely unlikely that a dental application will cause methemoglobinemia if used according to proper directions.

The Panel recommends that infants under 4 months of age should not be treated with benzocaine except under the advice and supervision of a dentist or physician. No specific warning concerning methemoglobinemia is considered necessary.

Objection to the use of benzocaine as an oral mucosal analgesic is contained in reports of allergic responses and cross reaction with other anesthetics derived from para-aminobenzoic acid (Refs. 3 and 13 through 21). However, the total number of cases of allergy is small compared to the total number of applications of the drug. In the North American Dermatologic Study (Ref. 20), the incidence of benzocaine irritancy and sensitivity equals that of other commonly used drugs and is less than that of the more frequent sensitizers. The Panel recommends that a warning on allergy be included on the label.

Because benzocaine is a derivative of para-aminobenzoic acid, it may interfere with sulfonamides when taken concurrently because benzocaine would theoretically inhibit the antibacterial action of sulfonamides (Refs. 3 and 4). No warning is recommended by the Panel since there has been no demonstration that the interaction with sulfa actually occurs under conditions of dental use.

(2) *Effectiveness.* There are studies documenting the effectiveness of 5 to 20 percent benzocaine in appropriate vehicles (Refs. 22 through 26).

Benzocaine is an effective topical anesthetic which has an almost immediate onset of action and a short duration. Adriani (Ref. 23) has shown 20 percent benzocaine in polyethylene glycol ointment to have an onset of 15 seconds when applied to oral mucosa. The effect can be prolonged by keeping the preparation in contact with the mucosa (Ref. 23). The pain-relieving action of benzocaine is entirely within the mucous membranes, since the quantity circulating in the blood is insufficient to provide analgesia or anesthesia to other areas.

After application of 20 percent benzocaine ointment to the tongue, electrical stimulation produced no response (Ref. 24). Concentrations below 5 percent have not been shown to be effective after oral topical application, and concentrations above 20 percent gave no further enhancement of anesthetic activity (Ref. 25). Thus, benzocaine in the range of 5 percent to 20 percent is considered effective.

Duration of effectiveness is directly related to duration of contact with the mucosa, but effectiveness is also dependent on the formulation of the preparation (Refs. 1, 18, 26, and 27). The Panel concludes that when properly formulated, benzocaine is effective as an oral mucosal analgesic for the relief of oral discomfort.

(3) *Dosage.* Adults and children 4 months of age and older: Apply 5 to 20 percent benzocaine in appropriate vehicles to the affected oral mucosal area not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

The Panal also recommends the following warnings for benzocaine:

(a) "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(b) "Fever and nasal congestion are not symptions of teething and may indicate the presence of infection. If these symptoms persist, consult your physician."

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b: *Butacaine sulfate.* The Panel concludes that a dosage of 0.75 g of a 4-percent ointment of butacaine sulfate is safe and effective for OTC use as an oral mucosal analgesic for the relief of oral discomfort as specified in the dosage section discussed below.

(1) *Safety.* Butacaine has a long history of use in dentistry (mainly under the supervision of a dentist) for denture sore spots and in extraction sites. Like other local anesthetics containing butyl groups, however, butacaine is highly toxic, having an $LD_{50}$ and a convulsant dose less than that of cocaine but greater than that of tetracaine (Ref. 1). Butacaine can be absorbed very rapidly from mucous membranes (Ref. 2); therefore, topical application is equivalent to systemic administration. Even in professional use a total dose of 10 ml of a 2-percent preparation or its equivalent (200 mg) should never be exceeded when application is made to the oral mucosa (Ref. 2).

The Panel recommends that the OTC dose should not exceed application of 30 mg of butacaine sulfate (0.75 g of 4 percent ointment), and this amount must be supplied in single-use units (no more than 6 units per package) so that the user will not exceed the safe dose. This dose and packaging are considered to be safe for OTC use on a risk-to-benefit ratio, but dosage and packaging containing larger amounts are unsafe for OTC use.

Irritancy tests in the hamster cheek pouch proved positive (Ref. 3); however, further studies of the ointment in guinea pigs and in humans demonstrated no irritancy (Refs. 3 and 4).

Although evidence is provided that butacaine has low allergenic potential, it is possible for subjects to be allergic to butacaine in rare cases (Ref. 3). Also, if a patient is allergic to procaine, he or she may show cross-allergy with butacaine because of close chemical similarities. Therefore, the patient should be warned not to use the product if allergic to procaine, butacaine, benzocaine, or other "caine" anesthetics.

(2) *Effectiveness.* Butacaine is an effective topical anesthetic with a long history of use (Refs. 5 through 15). Tainter and Moose (Ref. 6) claimed that, based upon effectiveness ratings and upon the lack of irritancy of its vehicle, butacaine was the most useful topical anesthetic in their study.

Butacaine is listed as an accepted drug in the 37th edition of "Accepted Dental Therapeutics" (Ref. 10). There is also other published evidence of the usefulness of butacaine for anesthesia in various clinical conditions of the mucosal surfaces of the eye, nose, throat, and mouth (Refs. 11 through 15).

(3) *Dosage.* Adults and children 12 years of age and older: Apply 30 mg (0.75 g of a 4-percent ointment) not more often than every 3 hours and not more than three applications daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

In addition, the Panel recommends the following warnings for butacaine sulfate:

(a) "Do not use on children under 12 years of age unless recommended by a dentist or physician."

(b) "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(c) "Do not use more than one unit at a time."

(d) "Do not repeat except after 3 hours."

(e) "Do not exceed 3 doses daily."

In addition, the labeling must not include the use of butacaine for teething pain.

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c. *Phenol preparations (phenol and phenolate sodium).* The Panel concludes

that 0.25 to 1.5 percent phenol in aqueous solution, up to 20 percent ethyl alcohol as a dental rinse, or up to 70 percent ethyl alcohol for direct application only, is safe and effective for OTC use as an oral mucosal analgesic for the relief of oral discomfort as specified in the dosage section discussed below.

(1) *Safety.* Clinical use and marketing experience have confirmed that aqueous phenol solutions are safe for application as an oral mucosal analgesic when used in concentrations ranging from a minimum of 0.25 percent to a maximum of 1.5 percent.

Maximum dosage should be restricted to that containing 600 mg within 24 hours for adults and children 12 years of age and older and 300 mg within 24 hours for infants and children 4 months to under 12 years of age.

The Panel reviewed reports that phenol and phenolic substances might have a carcinogenic or cocarcinogenic potential (Refs. 1 through 7). In addition to thorough study by the Panel, two experts were invited to consult with the Panel (Refs. 8 and 9).

Presentations by the consultants (Refs. 8 and 9) were especially helpful, since current views of earlier studies were presented. On the basis of data reviewed, the Panel concluded that if concentrations such as those recommended for mouth rinses or other OTC preparations are sufficiently low and the period of their use is restricted, there is no evidence that such use induces oral carcinoma (Refs. 3 and 8). The Panel determined that phenol should only be available at 1.5 percent or a lower concentration and that it should be limited to 7 days of continuous treatment, except under the supervision of a dentist or physician.

(2) *Effectiveness.* There are studies documenting the effectiveness of phenol as an oral mucosal analgesic (Refs. 10 through 14). Phenol has limited activity as a topical anesthetic. The local anesthetic activity of low concentrations is due to its ability to block nerve conductions (Refs. 10 and 11). However, if high concentrations are used, phenol demyelinates or otherwise destroys many types of nerve endings so that the ultimate action on nerve endings depends upon the concentration, contact time, and the vehicle used (Refs. 12 through 14).

(3) *Dosage*—(a) *Dental rinse.* 0.25 to 1.5 percent phenol in appropriate vehicles as directed. Dosage should not exceed 300 mg per day for children aged 6 to under 12 years. Dosage should not exceed 600 mg per day for adults and children aged 12 years and older.

(b) *Teething preparations.* 0.25 to 1.5 percent phenol in appropriate vehicles as directed. Dosage should not exceed 300 mg per day for infants and children 4 months to under 12 years of age.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

The Panel also recommends the following warnings for phenol preparations:

(a) "Fever and nasal congestion are not symptoms of teething and may indicate the presence of infection. If these symptoms persist, consult your physician."

(b) "Children between 6 and 12 years of age should be supervised in the use of this product as a dental rinse."

The labeling must also include adequate directions which will limit the dosage not to exceed 600 mg of phenol per day for adults and children 12 years of age and older and not to exceed 300 mg of phenol per day for infants and children 4 months to under 12 years of age.

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**Category I Labeling**

The Panel recommends the following Category I labeling for oral mucosal analgesic (topical anesthetic) active ingredients:

a. *Indications*—(1) *For all oral mucosal analgesics (topical anesthetics).* (a) "For the temporary relief of pain due to minor irritation or injury of soft tissue of the mouth."

(b) "For the temporary relief of pain due to minor dental procedures."

(c) "For the temporary relief of pain due to minor irritation of soft tissues caused by dentures or orthodontic appliances."

(d) "For the temporary relief of pain due to recurring canker sores when the condition has been previously diagnosed by a dentist."

(2) *For benzocaine and phenol used as oral mucosal analgesics (topical anesthetics) for teething pain.*

"For the temporary relief of sore gums due to teething in infants and children 4 months of age and older."

(3) *For oral mucosal analgesics (topical anesthetics) in denture adhesive products.*

"For the temporary relief of pain or discomfort of oral tissues due to dentures."

b. *Warnings*—(1) *For all oral mucosal analgesics (topical anesthetics).* (a) "Not to be used for a period exceeding 7 days."

(b) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(c) "Do not swallow."

(d) "Do not exceed recommended dosage."

(e) "Children under 12 years of age should be supervised in the use of this product."

(2) *For products containing "caine" derivatives.*

"Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacine, benzocaine, or other 'caine' anesthetics."

(3) *For products containing butcaine sulfate.*

(a) "Do not use in children under 12 years of age unless recommended by a dentist or physician."

(b) "Do not use more than one unit at a time."

(c) "Do not repeat except after 3 hours."

(d) "Do not exceed 3 doses daily."

(4) *For oral mucosal analgesics (topical anesthetics) for teething pain.*

"Fever and nasal congestion are not symptoms of teething and may indicate the presence of infection. If these symptoms persist, consult your physician."

(5) *For oral mucosal analgesics (topical anesthetics) in denture adhesive products.*

"See your dentist as soon as possible."

c. *Directions*—(1) *For products containing benzocaine.* Apply to the affected area not more than four times daily or as directed by a dentist or physician. For infants under 4 months of age there is no recommended dosage or treatment except under the advice and supervision of a dentist or physician.

(2) *For products containing butacaine sulfate.* Apply to the affected area. Do not use more than one unit at a time (each unit to contain no more than 30 mg butacaine sulfate). Do not apply more often than every 3 hours. Do not exceed three applications (90 mg) daily. Children under 12 years of age should not use this product except under the advice and supervision of a dentist or physician.

(3) *For products containing phenol.* (a) Apply to the affected area not more than six times daily. For adults and children 12 years of age and older, dosage should not exceed 600 mg of phenol per day. For infants and children 4 months to under 12 years of age, dosage should not exceed 300 mg of phenol per day. For infants under 4 months of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(b) For phenol formulated as a dental rinse, dosage should not exceed 600 mg of phenol per day for adults and children 12 years of age and older. For children 6 to under 12 years of age, dosage should not exceed 300 mg of phenol per day. For children under 6 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *For oral mucosal analgesics (topical anesthetics) in denture adhesive products.* Apply on area of denture that comes in contact with sore gums.

d. *Package limit.* Products containing butacaine sulfate should be packaged in single-use units to contain no more than 30 mg each with no more than six units per package.

2. *Category II conditions under which oral mucosal analgesic active ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC drug products for the relief of oral dicsomfort effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredients**

Camphor
Methyl salicylate

a. *Camphor.* The Panel concludes that camphor is not generally recognized as safe and effective for use as an OTC oral mucosal analgesic when applied topically to oral mucous membranes for the relief of oral discomfort. A camphor and phenol combination product was reviewed by the Panel. Although camphor was submitted as an active ingredient, the Panel considers phenol to be the active ingredient in this combination product, leaving camphor as a pharmaceutical aid which is intended to allow the use of a higher concentration of phenol.

(1) *Safety.* The Panel has reviewed copies of letters from Carol R. Angle, M.D., to the Hearing Clerk, FDA (Ref. 1) and to a former Director of FDA's Division of OTC Drug Evaluation (Ref. 2), a paper by W. J. Phelan (Ref. 3) which summarizes a report on poisoning by camphor products in 1974 by the National Clearinghouse for Poison Control Centers (Ref. 4), and a copy of the report on camphor from the minutes of the 16th meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Ref. 5). In general, that Panel's report concurred with this Panel's review of camphor regarding a pharmacological description of the ingredient and a discussion of its ingested toxicity. In particular, the report of the Miscellaneous External Panel cited numerous case studies of toxicity from camphor ingestions, most frequently of ingestions of camphorated oil, at least one of which goes back to 1848. The report of this Panel documents poisoning by solid camphor at even earlier dates.

In a number of instances, including those in the report submitted by Dr. Angle (Ref. 1), the ingested product contained one or more of other toxic substances in combination with camphor (Refs. 1, 2, and 3). In these instances it is difficult to ascribe the symptoms reported to only one agent. Gosselin et al. (Ref. 6) give camphor a toxicity rating of 4 (very toxic). However, many of the other combination ingredients, such as menthol, thymol, eucalyptol, methyl salicylate, and phenol, have also been given a toxicity raring of 4 by Gosselin et al. (Ref. 6). The 1974 report of the National Clearinghouse for Poison Control Center includes 244 ingestions of a combination product containing camphor and phenol and 89 ingestions of camphorated oil by children under 5 years of age (Ref. 4). As little as 0.7 to 1.0 g of camphor has proved fatal in children (Ref. 7). These data indicate that the problem of toxicity due to the ingestion of camphor is of current concern.

Phenol was accepted by the Panel for use at concentrations of 0.25 to 1.5 percent. A camphor-and-phenol-in-oil combination contains about 10 percent camphor and nearly 5 percent phenol. The research of Deichmann and associates (Refs. 8, 9, and 10) established that the presence of camphor-in-oil solutions of phenol brought into contact with an aqueous phase "holds" the phenol in the oil phase. In this way, the extent of the local action of phenol and the absorption of phenol through the tissues are considerably reduced from values found when phenol alone is present in this oil solution. The activity of camphor in this particular situation is that of a pharmaceutical necessity or pharmaceutical aid. Camphor is used for the same purpose (pharmaceutical aid) in camphorated parachlorophenol.

(2) *Effectiveness.* It is stated that camphor applied locally has a mild anesthetic action and that its application to the skin may be followed by numbness (Ref. 11). Phenol, when mixed with camphor, loses a great deal of its caustic effect but retains most of its analgesic and antiseptic action (Ref. 7).

The Panel considered whether or not there is any rationale for using a mixture of 4.66 percent phenol with 10.8 percent camphor (in liquid petroleum) to be applied in the mouth. Deichmann and Miller (Ref. 12) reorted that when a similar solution was equilibrated with an aqueous phase only 22 percent of the phenol entered the aqueous phase (equal to approximately 1 percent phenol in the aqueous phase). The availability of phenol may be more or less then 22 percent when the combination product is in contact with mucous membranes of the mouth. However, if one assumes that approximately 22 percent of the phenol in the combination enters the aqueous

phase and is available, then an aqueous solution of 1 percent phenol should probably be as useful as the phenol-camphor-liquid petrolatum combination used to relieve discomfort of minor irritation of oral soft tissues.

(3) *Evaluation.* The Panel concludes that the risk of accidental ingestion of camphor as well as phenol in the combination is not balanced by any increased benefit of the combination over use of small quantities of 1 percent phenol alone. The Panel therefore recommends that camphor be placed in Category II on the basis of the risk-to-benefit ratio. As an inactive ingredient the amount of camphor allowed to impart flavor or odor should be limited to less than 0.2 percent.

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b. *Methyl salicylate.* The Panel concludes that methyl salicylate is not generally recognized as safe and effective for OTC application as an oral mucosal analgesic.

(1) *Safety.* Methyl salicylate causes irritation with the possibility of local tissue damage when applied to mucous membranes (Refs. 1 and 2). Because of the reputed systemic toxicity of methyl salicylate, the Panel recommends that any dentifrice or dental care agent containing this substance as a pharmaceutical aid (i.e., flavoring agent) be in conformity with all pertinent regulations for its use as such.

(2) *Effectiveness.* There are no studies that indicate that topically applied methyl salicylate provides an anesthetic effect. It apparently acts only as a counterirritant (Refs. 2 and 3).

(3) *Evaluation.* Methyl salicylate is an irritant when applied topically, possibly causing local tissue damage. The Panel concludes that there is no rational use of methyl salicylate as an OTC oral mucosal analgesic.

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**Category II Labeling**

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of a product are unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

"For quick temporary relief of pain and soreness due to minor irritation of teeth and gums."

"Especially soothing after extractions or for minor gum boils."

"For temporary relief of cavity toothache."

"For rapid and effective relief of sore gums."

"For sore gums following tooth extractions."

"For use after teeth extraction."

"Hold in mouth as long and as frequently as necessary, then rinse." This is inconsistent with the directions of use proposed by the Panel.

"Eases pain due to cavities fast."

"Fast relief from toothache due to cavities."

"Temporary relief for toothache due to cavities."

"Gives quick relief that lasts for hours."

"For fast, temporary relief of minor mouth or gum soreness." The claim is too vague; it must be more specific.

"Subdues the throbbing ache of sore, swollen gums." The claim is too vague; gums may be infected or a deeper problem may exist.

"Stops baby's tears within seconds."

"Relief of discomfort of minor gum disorders before and after gingivectomy." Gingivectomy should be treated by a dentist.

The following claim encourages the consumer to avoid dental care by promoting use beyond the 7-day limit established by the Panel for safe use: "Holds dentures comfortably in place." This claim is acceptable when a denture adhesive is combined with an oral mucosal analgesic only for short-term use.

The Panel considers claims which imply a superiority in onset of action, such as "quicker," "more quickly," and "faster," to be misleading because all oral mucosal analgesics have a rapid onset.

The Panel considers the following terms to be vague and not definitive of the condition for which relief is sought: "sore spots," "anti-irritation," "comfortable adjustment," "helps comfortable adjustment," "stops pain," "soothes sore gums," "special," "unaccustomed use," "alleviates pain."

The following claims are for conditions that require the advice of a dentist: "gum boils," "gum or gingival inflammation," and "abscesses."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as noted for specific pharmacotherapeutic groups.

The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the ingredients and conditions listed below. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 2 years, however, the ingredients and conditions listed in this category should no longer be marketed in OTC products.

**Category III Active Ingredients**

Benzyl alcohol
Cresol

Thymol preparations (thymol and thymol iodide)

a. *Benzyl alcohol.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of benzyl alcohol at a concentration of 1 to 3 percent for OTC use as an oral mucosal analgesic for the relief of oral discomfort.

(1) *Safety.* There are insufficient data to establish the safety of 1 to 3 percent benzyl alcohol for OTC use as an oral mucosal analgesic.

Since animal studies suggest that ingestion of benzyl alcohol 1 mL/kg may be fatal (Ref. 1), and since package sizes that will provide more than 30 mL of a 2-percent solution or 60 mL of a 1-percent solution are unnecessary and may be a potential risk for accidental ingestion by young children, the Panel recommends that package size be limited to that containing a total of 0.6 mL of benzyl alcohol.

Benzyl alcohol in a 100-percent concentration is irritating to tissue; injected subcutaneously or intramuscularly the drug produces local necrosis (Refs. 1, 2, and 3). Benzyl alcohol given to dogs by stomach tube in doses of 0.2 to 0.5 mL/kg of body weight produced vomiting and defecation. These effects were attributed to local irritation of gastrointestinal mucosa because subcutaneous and intramuscular administration of these same doses did not produce these gastrointestinal reactions (Ref. 3). Benzyl alcohol applied to the tongue or lip of humans produces a primary irritating effect (Ref. 1). Instillation of the drug into the conjunctival sac of a rabbit was followed by some necrosis of the cornea (Ref. 1).

Benzyl alcohol in a concentration of 1 to 4 percent is included in injections, for subcutaneous or intramuscular administration, for its local anesthetic and bacteriostatic actions (Refs. 4, 5, and 6). Benzyl alcohol is categorized as a pharmaceutic aid (bacteriostatic) for injections in "National Formulary XIV," but the concentration to be used is not specified. Benzyl alcohol was categorized as a local anesthetic in the 10th, 11th, and 12th editions of the "National Formulary X." Category designation was begun with the 10th edition of the "National Formulary." In an early study, aqueous solutions of 1 to 3 percent benzyl alcohol were injected, apparently by infiltration, to provide local anesthesia for surgery in 33 patients (Ref. 1). This study reported that these solutions did not "produce any marked irritation or destruction of the tissues into which they were injected."

Upon application to the human cornea, 1 percent benzyl alcohol in isotonic saline produced transient pain described as "fairly severe smarting" (Ref. 7). Studies in which 1-percent or 1- to 4-percent solutions of benzyl alcohol were applied to corneas of experimental animals showed results varying from no irritation to reddening of the conjunctiva (Refs. 1 and 8). The more severe reactions were perhaps due to some deterioration of the benzyl alcohol under the conditions of storage. Since the drug is slowly soluble in water only to the extent of 1 g in 25 to 30 mL, aqueous preparations containing more than 3 to 4 percent benzyl alcohol are likely to contain some undissolved benzyl alcohol which may produce irritation (Refs. 4, 5, and 6).

There have been a few studies that evaluated the tissue irritation potential of benzyl alcohol in nonaqueous solvents. Application of 50 percent benzyl alcohol in 95 percent ethanol to the mucosa of the mouth or gums of 61 patients produced irritation in 31 percent of the patients and hyperemia in 11 percent of the patients (Ref. 9). That 50 percent benzyl alcohol was irritating is far from conclusive, however, because concurrently with the benzyl alcohol solution tests, 95 percent ethanol was applied on the opposite side of each patient's mouth. The ethanol "control" produced irritation in 40 percent of the patients and hyperemia in 18 percent of the patients. In a subsequent report of 156 patients who were tested with 95-percent ethanol, 38 percent responded with irritation and 14 percent with hyperemia; of 506 "aqueous controls," 14 percent showed irritation and 7 percent showed hyperemia (Ref. 10). In addition to the 506 patients treated with "aqueous control" (water or 0.9-percent sodium chloride solutions with color or a flavor or "fluorescent"), 70 patients were treated with "Liquor Alkalines Aromaticus," "National Formulary V." or "National Formulary VI." Since this solution may possibly be irritating, these patients were not included in the figures stated in this document.

A preparation containing 1 percent benzyl alcohol, together with benzocaine and clove oil, in an adhesive base intended for application to the oral mucous membrane, was subjected to sensitization and irritation tests (Ref. 11). At the 24-hour and subsequent observation periods after application of the material to the skin, eyes, and oral mucous membranes of experimental animals, no irritation was observed. However, no data were presented on any observations prior to the 24-hour period. Guinea pig sensitization tests were negative.

The studies cited above show that undissolved benzyl alcohol is a potent irritant. Aqueous solutions in concentrations from 1 to 3 percent of benzyl alcohol may produce variable degrees of irritation to soft tissues.

(2) *Effectiveness.* Benzyl alcohol does possess local anesthetic activity, but the concentrations (in aqueous and nonaqueous solvents) needed to provide relief of pain of oral soft tissues have not been established. Standard reference sources attribute local anesthetic activity to benzyl alcohol and cite uses by injection, by application to mucous membrances, and by application to the skin as an antipruritic (Refs. 4, 5, and 6). For OTC dental and related use, benzyl alcohol is included in preparations for toothache, for sore mouth due to dentures, and for cold sores.

Two to 4 percent benzyl alcohol in saline produced anesthesia in dogs when injected subdurally (Ref. 13). Concentrations of 1 to 3 percent benzyl alcohol were injected to provide anesthesia for surgical procedures apparently be infiltration in 33 humans (Ref. 1).

Topical applications of solutions of benzyl alcohol are reported to be uncertain in effect (Ref. 4). In descriptive, uncontrolled studies in experimental animals and humans, benzyl alcohol applied topically in 1- to 2-percent solutions was reported to produce complete or partial anesthesia of skin (Refs. 1 and 7), motor nerves, and sensory nerves of frogs (Ref. 1); corneas of animals (Refs. 1, 7, and 8); and oral mucous membranes of humans (Refs. 1 and 7). In another uncontrolled study, a 10-percent solution of benzyl alcohol applied to the tip of the tongue of human subjects provided a short period of anesthesia (Ref. 14). Application of pure benzyl alcohol to the nostrils, skin, tongue, or lips of humans was followed by some degree of anesthesia (Refs. 1 and 7).

In the only controlled, double-blind studies of local anesthetic activity of topical benzyl alcohol which could be found in the literature, a 50-percent solution of benzyl alcohol in 95 percent ethanol was compared with placebo aqueous solutions and with 95 percent ethanol without benzyl alcohol (Refs. 9 and 10). The solutions were applied to the oral mucous membranes of humans. Complete or partial anesthesia was reported by 43 percent of the 576 patients receiving various placebo aqueous solutions, 78 percent of the 156 patients receiving 95 percent ethanol

solutions and 79 percent of the 61 patients treated with 50-percent benzyl alcohol in 95 percent ethanol (Ref. 10). In the initial study in this series, patients were concurrently treated on opposite sides of the mouth with 50 percent benzyl alcohol in 95 percent ethanol and with 95 percent ethanol (Ref. 9). Of the 61 patients tested, 67 percent experienced complete or partial anesthesia with 95 percent ethanol and 79 percent reported some anesthesia with 50 percent benzyl alcohol in 95 percent ethanol. No statistics were presented, and the benzyl alcohol concentration was very high.

Since benzyl alcohol solutions stored in soft glass containers have been shown to increase in pH and decrease in anesthetic activity, the Panel believes there may be stability problems with benzyl alcohol solutions in some dosage forms or in some types of packaging. Therefore, the stability of benzyl alcohol in the particular dosage form and packaging intended for marketing should be established (Ref. 8).

(3) *Proposed dosage.* Adults and children 2 years of age and older: Apply 1 to 3 percent benzyl alcohol to the affected area not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

In addition, products containing benzyl alcohol should contain no more than a total of 0.6 mL (30 mL of a 2-percent solution or 60 mL of a 1-percent solution) of benzyl alcohol in a container capable of maintaining stability of the product.

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the safety and effectivenesss of 1 to 3 percent benzyl alcohol as an oral mucosal analgesic. Data to demonstrate safety and effectiveness as an oral mucosal analgesic will be required in accordance with the guidelines set forth below. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(5) Blacow, N. W., and A. Wade, "Martindale: The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, pp. 50–51, 1972.

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(7) Sollman, T., "Benzyl Alcohol: Its Anesthetic Efficiency for Mucous Membranes," *Journal of Pharmacology and Experimental Therapeutics,* 13:355–360, 1919.

(8) Macht, D. I., and A. T. Shohl, "The Stability of Benzyl Alcohol Solutions," *Journal of Pharmacology and Experimental Therapeutics,* 16:61–69, 1921.

(9) Tainter, M. L., and M. Moose, "Studies in Topical Anesthesia: I. The Efficacy of Certain Common Anesthetics when Used on the Gums," *Journal of the American Dental Association,* 23:244–250, 1936.

(10) Tainter, M. L., A. H. Throndson, and S. M. Moose, "Studies in Topical Anesthesia: II. Further Observations on the Efficacy of the More Common Local Anesthetics When Used on the Gums and Oral Mucosa," *Journal of the American Dental Association and Dental Cosmetics,* 24:1480–1487, 1937.

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(12) Voegtlin, C., and A. E. Livingston, "Benzyl Alcohol as a Spinal Anesthetic," *Journal of Pharmacology and Experimental Therapeutics,* 13:513, 1919.

(13) Adriani, J., et al., "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics,* 5:49–62, 1964.

b. *Cresol.* The Panel concludes that there are insufficient data available to permit the final classification of the safety and effectiveness of cresol at a concentration of 0.25 to 1.0 percent for OTC use as an oral mucosal analgesic for the relief of oral discomfort.

(1) *Safety.* Cresol, a mixture of 2-, 3-, 4-methylphenols, is obtained by fractional distillation of coal tar or petroleum (Refs. 1 and 2). Cresol is a protoplasmic poison resmbling phenol in its effects, although it may be slightly more corrosive than phenol and its systemic effects may be slightly milder because of slower absorption (Refs. 3 and 4). In an invitro test, 0.25 percent cresol, 0.54 percent phenol, 0.3 percent *m*-cresol, and 1.2 percent benzyl alcohol produced total hemolysis of erythrocytes (Ref. 5). In a study of carcinogenic activity of phenol and related compounds on mouse skin, each of the three cresols was reported to have the same order of "promoting" activity as phenol (Ref. 6).

On the skin, cresol produces erythema, burning, and numbness (Ref. 2). If ingested, cresol causes a severe burning sensation in the mouth and upper abdomen, dysphagia (difficulty in swallowing), vomiting, and diarrhea (Ref. 2). Chronic poisoning (either by ingestion or percutaneous absorption) may produce widely varied reactions such as gastrointestinal disturbances, central nervous system dysfunctions, skin eruptions, jaundice, oliguria, and uremia (Ref. 7). At least one death has been reported from topical application of cresol to a large area of the body surface of a child (Ref. 8). Irritation of periapical tissues may occur if cresol is used in root canal therapy (Ref. 1).

Dilute solutions of cresol are used in therapeutics, although the Panel found no data relating to safety of such solutions. Cresol is sometimes used in concentrations of 0.25 to 0.5 percent as a bacteriostatic agent in parenteral solutions. A saponated solution containing 0.5 percent cresol has been used for application to wounds, and a saponated solution containing 0.1 percent cresol has been used as a vaginal douche (Ref. 2).

The maximum dosage for cresol should be restricted to no more than 400 mg within 24 hours for adults and children over 12 years of age and 200 mg within 24 hours for children 6 to 12 years of age.

(2) *Effectiveness.* Early studies in experimental animals and man suggest that cresol solutions have some local anesthetic activity (Refs. 9 through 12). Gurney (Ref. 13) reports that cresols have been used as mild pulpal analgesics and that they exhibit a demonstrable analgesia when applied under proper conditions. He notes that the analgesia may be easily seen with application of cresol to irritated pulps of primary teeth, but it is very difficult to demonstrate analgesia with permanent teeth. Gurney's paper (Ref. 13) did not include clinical studies.

The Panel conducted a thorough search of the scientific literature for clinical studies of cresol as a local anesthetic for use on soft oral tissue. Such studies were not found. One submission included one unpublished clinical study of the obtundent qualities of a product containing cresol and boric acid (Ref. 14). This clinical study apparently included more than 120 patients, but it was uncontrolled, not well documented, and evaluations were subjective.

(3) *Proposed dosage.* Adults and children 6 years of age and older: Apply 0.25 to 1.0 percent cresol in aqueous solution to the affected area. The total amount to be applied in a 24-hour period should not exceed 400 mg for adults and

children over 12 years of age or 200 mg for children 6 to 12 years of age.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling).

In addition, the panel recommends the following warning for cresol:

"Do not use in children under 6 years of age unless recommended by a dentist or physician."

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the safety and effectiveness of cresol as an oral mucosal analgesic. Data to demonstrate safety and effectiveness of cresol as an oral mucosal analgesic will be required in accordance with the guidelines set forth below. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 209, 1977.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 355, 1973.

(3) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 63, 1977.

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(14) OTC Volume 080013.

c. *Thymol preparations (thymol and thymol iodide).* The Panel concludes that thymol preparations in concentrations up to 20 percent are safe but that there are insufficient data available to permit final classification of their effectiveness of OTC use as oral mucosal analgesics.

(1) *Safety.* The acute toxicity of thymol in a solution of propylene glycol was determined by oral administration to experimental animals (Ref. 1). Groups of 10 young adult Osborne-Mendel rats, evenly divided by sex, were fasted for approximately 18 hours and given the test material. The $LD_{50}$ was 0.98 g/kg with a death time ranging from 4 hours to 5 days. The toxic signs with high dose consisted of depression, ataxia (irregularity of muscle action), and coma.

The minimum lethal dose of thymol when administered by the oral route has been reported to be 800 mg/kg in the mouse, 750 to 1,000 mg/kg in the rabbit, and 250 mg/kg in the cat (Ref. 2).

Thymol is considered to be less toxic than phenol. In humans fats and alcohol increase absorption and aggravate the toxic symptoms (Ref. 3). Thymol is completely absorbed from the intestine. It is excreted in the urine as the sulfate and glucuronide together with some thymol-quinone. About half of a dose is destroyed in the body. Thymol is an irritant to the kidney (Ref. 3).

There are no apparent studies on thymol iodide; however, when thymol iodide was fed to rats for 5 weeks in a study designed to demonstrate iodide availability, there was considerable uptake of iodide by the thyroid (Ref. 4).

Boutwell and Bosch (Ref. 5) studied over 50 compounds related to phenol for their ability to promote the development of skin tumors following a single initiating dose of dimethylbenzanthracene. One of these compounds tested (2-isopropyl-4-methyphenol) is closely related to thymol. When dissolved in 16 percent benzene and applied weekly for 12 weeks to mice, 19 percent developed skin tumors and 6 percent (1 of 16 mice) developed a carcinoma.

"The United States Dispensatory" (Ref. 6) states that thymol can cause nausea, vomiting, albuminuria, headache, tinnitus, dizziness, muscular weakness, a thready pulse, slow respiration, and a fall in body temperature. It further states that the heart is depressed by "therapeutic" doses. Thymol, used systemically in the treatment of mycosis, has been given as divided oral doses consisting of 1 to 2 g daily being administered in courses of 2 of each 3 days. It has also been used as an intestinal antiseptic, in doses up to 120 mg.

Gleason et al. (Ref. 7) state that the toxicity of thymol is believed to lie on the borderline between toxicity classes 3 and 4 (moderately toxic and very toxic).

Thymol is less toxic than phenol and larger doses may be taken (Ref. 3). It is generally an irritant to tissues, and given orally it is an irritant to the gastric mucosa. Rashes from thymol are not uncommon (Ref. 3). It was formerly used for the treatment of hookworm infestations, but had to be used in such large doses that there was danger of serious, even fatal, poisoning. Oral doses stimulate peristalsis and may cause diarrheal stools (Ref. 6).

Thymol should not be given by mouth to persons with gastrointestinal disorders or impared kidney function. It should be given with care to patients with heart disease (Ref. 3). However, the amounts used topically in the oral cavity are insufficient to cause problems for these individuals.

(2) *Effectiveness.* Thymol is used chiefly as a deodorant in antiseptic mouthwashes and gargles. Mixed with phenol and camphor, thymol is used in dentistry to prepare cavities before filling, and it is mixed with zinc oxide to form a protective cap for the dentine (Ref. 3).

There are reports of use of thymol or thymol iodide in oral mucosal analgesic products, but there are insufficient data to establish effectiveness (Refs. 1 through 7). Since eugenol and thymol are chemically similar, the possibility of effectiveness as an oral mucosal analgesic is suggested and has, in fact, been frequently associated with professional use for this purpose (Ref. 3).

(3) *Proposed dosage.* Adults and children 2 years of age and older: Apply a maximum of 20 percent thymol or thymol iodide to the affected area not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the effectiveness of thymol preparations as oral mucosal analgesics. Data to demonstrate effectiveness as an oral mucosal analgesic will be required in accordance with the guidelines set forth below. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

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**Category III Labeling**

None.

*C. Data Required for Evaluation*

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

Adriani et al. (Ref. 1) have studied surface anesthetic activity in great depth, and their research provides a methodology which the Panel recommends for testing oral mucosal analgesics. The selection of patients, study method, and interpretation of data are also included in these investigations and should serve as a model.

In addition, data to demonstrate safety of cresol and benzyl alcohol should include well-designed studies demonstrating lack of irritation of oral mucous membranes in humans under conditions of proposed use.

The Panel concludes that 3 years after publication of the proposed rules is an adequate time period for the completion of studies and the submission of data.

**Reference**

(1) Adriani, J., et al., "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics*, 5:49–62, 1964.

**V. Oral Mucosal Protectants**

*A. General Discussion*

Oral mucosal protectants are insoluble, pharmacologically inert substances that form adherent, continuous, flexible, or semirigid coats when applied to the oral mucous membranes (Ref. 1). These coatings help to protect the irritated areas of the mouth from further irritation from chewing, swallowing, and other mouth activity. When applied locally to the oral mucous membranes, they can provide temporary relief of discomfort of minor thermal or chemical burns, irritations, or ulcerations resulting from mechanical trauma and aphthous ulcerations (canker sores).

Oral mucosal protectants may be applied by health professionals such as dentists or physicians in treating their patients, or they may be applied as self-medication by the patients themselves. The Panel has considered the various conditions where such protectants might be used professionaly and on a self-medication basis. The Panel concludes that oral mucosal protectants available as OTC products may be locally applied to oral mucous membranes for the temporary relief of discomfort from minor burns of the oral mucosa and minor injuries or irritations of the mouth. The Panel also concludes that the treatment of persistent aphthous ulcerations and other mouth ulcerations depends upon a professional diagnosis and that such treatment should be under the advice of a dentist or physician. Therefore, OTC labeling should include the use of a protectant for these indications only if the condition has been previously diagnosed by a dentist or physician. (See part V. paragraph B.1. below—Category I Labeling.)

It is possible that solutions of protective substances might serve as carriers of other medicinal materials. For example, an oral mucosal analgesic such as benzocaine might be included in the formulation to add its effect to the protectant in relieving pain from irritation.

Benzoin tincture and compound benzoin tincture are generally recognized as effective as oral mucosal protectants by the Panel on the basis of published observations by dental experts. (See part V. paragraph B.1. below—Benzoin preparations (benzoin tincture and compound benzoin tincture).)

The effectiveness of Category III protectants must be established by demonstrating that the agent provides a suitable coating when applied to the oral mucosa protecting minor irritations and injuries from further irritation. Effectiveness should be established by 2 well-controlled clinical studies, and 2 years should be allowed for such studies. (See part V. paragraph C. below—Data Required for Evaluation.)

**Reference**

(1) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 712–714, 1975.

*B. Categorization of Data*

1. *Category I conditions under which oral mucosal protectant active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

**Category I Active Ingredient**

Benzoin preparations (benzoin tincture and compound benzoin tincture)

*Benzoin preparations (benzoin tincture and compound benzoin tincture).* The Panel concludes that benzoin preparations are safe and effective for OTC use as oral mucosal protectants for the relief of oral discomfort as specified in the dosage section discussed below.

For the purpose of this review, compound benzoin tincture is considered as a single entity since the proportion of ingredients has been fixed over many decades. Also, the Panal does not differentiate the safety and effectiveness data of benzoin tincture and compound benzoin tincture. Compound benzoin tincture, which is official in the "United States Pharmacopeia" (Ref. 1), contains 10 percent benzoin, 2 percent aloe, 8 percent storax, 4 percent tolu balsam, and 74 to 80 percent ethanol (Ref. 1). Benzoin tincture contains 20 percent benzoin and 75 to 83 percent alcohol. Benzoin tincture is no longer official, but it is still available on the market in the United States.

(1) *Safety.* Clinical use and marketing experience have confirmed that benzoin preparations are safe for OTC use. There is little information in the literature on the safety and toxicity of benzoin and the other constituents that make up the compound tincture.

Gosselin et al. (Ref 2) assigns benzoin, storax, and tolu toxicity ratings of 3 (moderately toxic); aloe or aloin has a toxicity rating of 4 (very toxic) when ingested orally. Drugs with a toxicity rating of 3 are considered to have probable lethal dosage of 500 mg to 5 g/kg body weight. Drugs with a toxicity rating of 4 are considered to be probably lethal in doses of 50 to 500 mg/kg body weight.

Although the toxicity ratings are given on the basis of the ingredients of the tincture and the compound tincture, Gosselin et al. (Ref. 2) state that alcohol is expected to be responsible for the major toxic effects of ingestion of these tinctures.

No reports giving evidence of chronic toxicity of benzoin, storax, aloe, and tolu were found in the literature.

Hypersensitively and irritation from topical use of the benzoin tinctures were reported in two papers. In a study involving 413 patients with contact dermatoses, it was found that two showed allergic reactions to patch tests of compound benzoin tincture (Refs. 3 and 4). Another report states that a 22-year-old man exhibited sensitivity to benzoin and to other gums and resins when given a patch test (Refs. 3 and 5). He had previously developed acute eczematous contact dermatitis 23 days following the application of benzoin tincture to the skin under a plaster cast. A patch test also demonstrated cross-sensitivity to myrrh.

Dental clinicians have, however, been using and recommending benzoin tinctures for topical application to oral tissues for many years, and the use has apparently been without adverse effects. Furthermore, very small quantities of the tinctures are used per application when applied locally to oral mucous membranes. In spite of the high alcohol content, benzoin tincture and compound benzoin tincture are considered safe for occasional application to small areas of the oral mucosa.

Tinctures of benzoin should be packaged in well-closed containers of 30 mL or less and have child-proof caps.

(2) *Effectiveness.* There are studies documenting the effectiveness of compound benzoin tincture (Refs. 3 and 6 through 21). In the treatment of intraoral lesions, the tissues are first dried because benzoin is not water soluble, and then the tincture is applied. In this manner a protective, although transient, coating is deposited on the area of application. Although there are no double-blind, well-controlled clinical studies to support the effectiveness of the benzoin tinctures as protectants, the use of benzoin tincture and compound benzoin tincture for the treatment of lesions of oral mucous membranes has been successful for a long time in dentistry. Standard references list a number of dental uses for benzoin tinctures in providing relief from oral discomfort. The tincture or the compound tincture used full strength, though often mixed with glycerin and water, is applied locally as a protective in small cuts, cutaneous ulcers, and fissures of the lips (Refs. 2 and 6 through 9). Applied full strength, the tinctures are said to have protective, stimulating, and styptic activity (Refs. 3, 8, and 10).

Benzoin tincture has been used for pulp capping and for saturating intraoral dressings used in treatment of painful extraction wounds (Refs. 8 and 11). Application of compound benzoin tincture has been widely recommended as a protective for relief of discomfort of chemical or thermal burns (Refs. 12 through 15), of minor mechical or physical trauma (Refs. 14, 15, and 16), and of irritations of the oral mucosa (Refs. 9 and 17).

Compound benzoin tincture has also been recommended as a protective for relief of discomfort from aphthous ulcers (Refs. 3, 6, 7, 18, and 20) and of oral herpes simplex ulcers (Refs. 7, 10, and 21). The Panel has concluded, however, that recurring aphthous stomatitis (canker sores) is an OTC indication for protectives only if the condition has been previously diagnosed by a dentist or physician. Indications for oral herpes simplex ulcers were deferred to the Advisory Review Panel on OTC Miscellaneous External Drug Products.

Benxoin tincture and compound benzoin tincture should only be used as a single ingredient at full strength, because combining benzoin with another ingredient will dilute the product and reduce its effectiveness as a protectant. Literature cited has described only the use of full-strength tinctures as protectives in applications to the oral mucosa. Effectiveness of tinctures with concentrations less than full/strength remains to be shown.

(3) *Dosage.* Adults and children 6 months of age and older: Apply to the affected area undiluted not more often than every 2 hours.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

**References**

(1) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, p. 51, 1975.

(2) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, pp. 156–157 and 166, section III, pp. 140–143, 1976.

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**Category I Labeling**

The Panel recommends the following Category I labeling for oral mucosal protectant active ingredients:

a. *Indications.* (1) "Forms a coating over a wound."

(2) "Protects against further irritation."

(3) "For temporary use to protect wounds caused by minor irritations or injury."

(4) "For protecting recurring canker sores when the condition has been previously diagnosed by a dentist."

b. *Warnings.* (1) "Not to be used for a period exceeding 7 days."

(2) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(3) "Do not swallow."

(4) "Do not exceed recommended dosage."

(5) "Children under 12 years of age should be supervised in the use of this product."

c. *Directions.* For adults and children 6 months of age and older: Dry the affected area, saturate a cotton applicator with medication, and apply to the affected area not more often than every 2 hours. For children under 6 months of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

d. *Package limit.* Products containing tinctures of benzoin should be packaged in well-closed containers of 30 mL or less and should have child-proof caps.

2. *Category II conditions under which oral mucosal protectant active ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC relief of oral discomfort drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredients**

None.

**Category II Labeling**

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of a product are unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

"Especially soothing after extractions or for minor gum boils."

"Gives quick relief that lasts for hours."

"For fast, temporary relief of minor mouth or gum soreness," This claim is too vague.

"For rapid and effective relief of sore gums."

"Subdues the throbbing ache of sore, swollen gums." Claim is too vague, gums may be infected or a deeper problem may exist.

"Relief of discomfort of minor gum disorders before and after gingivectomy." Gingivectomy should be treated by a dentist.

The Panel considers the following terms to be vague and not definitive of the conditions for which relief is sought: "sore spots," "anti-irritation," "comfortable adjustment," "helps comfortable adjustment," "stops pain," "soothes sore gums," "special," "unaccustomed use," "alleviates pain."

The following claims are for conditions that require advice of a dentist: "gum boils," "gum or gingival inflammation," and "abscesses."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as noted for specific pharmacotherapeutic groups.

**Category III Active Ingredient**

Myrrh, fluidextract

*Myrrh, fluidextract.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of myrrh, fluidextract for OTC use as an oral mucosal protectant for the relief of oral discomfort.

(1) *Safety.* No reports of acute or subacute toxicity of myrrh were found. In a pharmacological study, addition of myrrh to oxygenated Locke solutions containing segments of intestines from rabbits or cats resulted in paralysis of the intestinal muscle (paralysis indicated by relaxation of muscle tonicity, inhibition of contractions, and little or no response to subsequent treatment with pilocarpine) (Ref. 1). Locally, myrrh is reported to be stimulating and for this reason may excite peristalsis if ingested (Refs. 2, 3, 4, and 5). Myrrh has been used as an ingredient in certain cathartic pills, e.g., aloe and myrrh pills. (Ref. 6).

Although reports of hypersensitivity were not found, myrrh and benzoin may be cross-sensitizing. In one report, a 22-year old man developed acute eczematous contact dermatitis 23 days following the application of benzoin tincture to the skin under a plaster cast. In later patch tests, he demonstrated sensitivity to benzoin and cross-sensitivity to myrrh, locust, galbanum, gemboge and olibanum (Refs. 3 and 7).

(2) *Effectiveness.* Myrrh tincture applied locally to mucous membranes of the mouth and throat has been reported to have an astringent action, a stimulating action, or stimulating and protective action (Refs. 2 through 5, and 8). Myrrh has been used in treating various disorders of the mouth and throat including spongy gums, aphthous stomatitis, and ulceration of the mouth and throat (Refs. 2, 3, and 5). In addition to being applied in the form of the tincture, myrrh is sometimes used in mouthwashes and gargles (Refs. 2, 9, and 10).

Protectives should be designed to cover the mucous membranes in order to prevent contact with possible irritants. There are no clinical studies to support the effectiveness of myrrh as a protectant. Myrrh is usually applied locally as an alcoholic solution such as the tincture which contains 83 to 88 percent alcohol. Upon evaporation of the alcohol, a water-insoluble protective coating over the area might be left. However, myrrh is also used in the form of a lotion or gargle, prepared by mixing myrrh tincture with aqueous fluids (Refs. 2, 9, and 10). When the tincture is mixed with aqueous fluids a good portion of the myrrh will precipitate out (Ref. 9). Particulate matter from such a gargle would not serve as a protective. Any benefits would have to be derived from other constituents in the drug.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Apply 0.2 to 0.3 ml myrrh, fluidextract, directly to affected area.

(4) *Labeling.* The Panel recommends the Category I labeling above for oral mucosal protectant active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the safety and effectiveness of myrrh, fluidextract, as an oral mucosal protectant. Data to demonstrate safety and effectiveness as an agent for the relief of oral discomfort will be required in accordance with the guidelines set forth below. (See part V. paragraph C. below—Data Required for Evaluation.)

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**Category III Labeling**

None.

*C. Data Required for Evaluation*

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

There are no good, generally accepted protocols for testing an oral mucosal protectant. One of the major factors is that the ingredients in this pharmacologic group can be used for a number of different conditions of different etiology. Industry and FDA must cooperate on developing suitable testing methods.

One of the important indications for the use of a protectant is to protect an area of injury or disease from painful stimuli. Areas ordinarily amenable to such therapy are isolated or discrete areas rather than large areas, as one sees in acute herpetic gingivostomatitis; examples of target areas are isolated herpetic lesions and those of aphthous ulcers which occur singly and at infrequent intervals. Other indications would be allergic reactions, abrasions, burns, and oral wounds of a variety of origins.

A protectant, in any of the above conditions, must shield the area from painful stimuli for a reasonable period of time. The protectant must be easily applied to the involved area, must attach to oral mucous membranes and be resistant to saliva and salivary flow. The painful stimulus which is to be obtunded may arise from either thermal (hot or cold), chemical (acid, base, or other), or physical (abrasive foods) sources.

Although protection from painful stimuli would be one of the best measures of effectiveness, the likelihood of finding a test population with standard lesions, in similar areas, at the same stage of development, is very small. Aphthous ulcers, for example, are painful, last 7 to 10 days, and usually heal uneventfully. The amount of pain gradually decreases from the first day to the 10th day, so that the level of pain response to any stimulus would vary with the state of development, making standardization among subjects very difficult.

In view of these difficulties, methods must be developed to measure by physical means the ability of a protectant to adhere to mucous membranes and to resist solution in and by saliva. Such methods may include the use of fluorescent dyes over a minimum time period as an indicator of penetration and protection. Changes in volume displacement may be a useful indicator.

In addition, since there is very little information on either the safety or the toxicity of myrrh, it is impossible to evaluate the safety of the drug. The manufacturers should, therefore, submit data from controlled studies including:

1. Acute and subacute studies ($LD_{50}$) in more than one species.

2. Chronic studies involving the addition of myrrh in the diets of experimental animals for periods longer than 60 days.

3. Irritation studies involving the application of myrrh in appropriate concentrations to normal and inflamed or irritated mucosal tissues. Both acute and chronic studies should be performed.

**VI. Tooth Desensitizers**

*A. General Discussionge*

Tooth desensitizers are agents used to treat "hypersensitive" (ultrasensitive) dentin. This condition sometimes develops when dentin is exposed to the environment of the oral cavity. The dentin, which contains the sensory mechanism of the tooth, is normally covered by either enamel (crown) or cementum (root). When the latter calcified structures are absent as a result of erosion, abrasion, removal by the dentist, a defect in the tooth, or some other cause, the resultant exposed dentin can become ultrasensitive to various stimuli. Temperature change, mechanical stimuli, and certain chemicals may then induce a painful response. The interpretation of the cause of hypersensitive dentin is complex for several reasons: (1) Dental restorations may transmit temperature changes, (2) carious teeth are sensitive to similar stimuli, and (3) a tooth with pulpal degeneration may be sensitive to temperature changes. The dentist may make the diagnosis of hypersensitive dentin if all carious lesions have received professional treatment, if there are no restorations causing the ultrasensitive response, and if there are no symptoms suggestive of pulpal damage.

Even though the consumer cannot self-diagnose dental hypersensitivity and must obtain professional advice, it is still considered useful by the Panel to have tooth desensitizers available as an OTC product for temporary use until a dentist can be seen or after a dentist has diagnosed dental hypersensitivity. It is estimated that there is a significant target population with hypersensitive dentin which would use an OTC dentifrice for desensitization (Ref. 1). Therefore, the Panel recommends that these products be made available to the public with a warning that unless recommended by a dentist, the products are to be used for not more than 2 weeks. The labeling should include appropriate statements on the dangers of neglecting dental care. (See part VI. paragraph B.1 below—Category I Labeling.)

The problems involved in evaluating dentifrices which make the desensitization claim are manifold. The first problem is that of diagnosis as mentioned above. Second, the problem of the mechanism of action of dentin desensitizers is compounded by the currently limited knowledge of normal dentin sensation. Seltzer (Ref. 2) in 1971 reviewed current hypotheses of dentin sensitivity to thermal, tactile, chemical, and electrical stimuli and concluded that basic mechanisms of dentin sensitivity have not been completely elucidated. Everett, Hall, and Phatak (Refs. 1 and 3) state that while the rationale of desensitization procedures is not fully understood, some agents may depend upon denaturation of the superficial ends of Tomes' fibers or of nerve endings in dentin. Other agents may act by depositing an insoluble substance in the ends of the fibers or nerves and thus may act as a barrier to stimuli and still other agents may act by stimulating irritational dentin formation. It is apparent that evaluation of desensitizing agents must be made, at this time, without complete information on the precise mechanism of action. Third, the task of evaluating desensitizing agents is made difficult by the methods of testing which have been

employed. Both thermoelectric and mechanical stimuli have been used in attempts to objectively measure responses. It has been found in numerous studies that it is difficult to objectively measure the subjective response to pain. Other studies to evaluate dentin desensitizers are based upon the patient's subjective response. Craig (Ref. 4) made a strong point in favor of the latter evaluative method when he found that thermal and mechanical stimuli were so poorly tolerated by patients that it was felt that use of such devices may have resulted in false readings arising from anticipation of discomfort. However, Smith and Ash (Ref. 5) made no mention of lack of cooperation by patients when thermoelectrical and mechanical devices were used to measure responses and further noted no significant correlation between a subject's impression of change in sensitivity and actual change in sensitivity as determined by application of quantitative stimuli. The reporting of the degree of relief of hypersensitivity may be either in the form of improvement versus no improvement or various other qualifying statements such as complete, good, moderate, fair, or poor. Thus, comparisons between various studies are difficult.

It is also important to note that the time-course of studies varies considerably, and some agents appear to be more or less effective depending upon the period of time a patient has been using that particular agent (Ref. 6).

Some identifiable causes of tooth sensitivity which would not be relieved by desensitizing agents include microscopic cracks in teeth, inflammation of the pulp, occlusal trauma (injury due to biting), and recently placed restorations. In cases in which the dentin is definitely exposed, there are still multiple causes for the exposure, such as abrasions caused by toothbrushing or other factors, eroding chemicals, exposure due to periodontal surgery, or defective enamel formation. From these many causes, one would expect different quantitative, as well as qualitative, effects of the desensitizers under different conditions.

In view of this background of confusing data and facts, the Panel does not recommend classifying any ingredients in Category I with a claim for desensitization. Further study of tooth desensitizers is recommended utilizing the guidelines which are discussed later in this document. (See part VI. paragraph C. below—Data Required for Evaluation.)

**References**

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*B. Categorization of Data*

1. *Category I conditions under which tooth desensitizer active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federl Register.**

**Category I Active Ingredients**

None.

**Category I Labeling**

The Panel recommends the following Category I labeling for tooth desensitizer active ingredients:

a. *Indication.* "To aid in the reduction of painful sensitivity of the teeth to cold, heat, acids, sweets, or contact."

b. *Warnings.* (1) "Do not continue use beyond 2 weeks except under supervision of a dentist."

(2) "Do not swallow."

(3) "Children under 12 years of age should be supervised in the use of this product."

(4) "Sensitive teeth may indicate a serious problem which needs prompt care by a dentist."

(5) "See your dentist as soon as possible whether or not relief is obtained."

c. *Directions.* Apply with a toothbrush at least once a day or as recommended by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

2. *Category II conditions under which tooth desensitizer active ingredients are not agenerally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC drug products for the relief of oral discomfort effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredients**

Sodium fluoride (0.44 percent), strontium chloride, and edentate disodium (in combination)

*Sodium fluoride (0.44 percent), strontium chloride, and edetate disodium (in combination).* The Panel concludes that the combination of sodium fluoride (0.44 percent), strontium chloride, and edetate disodium is not generally recognized as safe and effective for OTC use as a tooth desensitizer.

In the product submitted, sodium floride and strontium chloride are kept in solution by means of edetate disodium which chelates strontium and prevents formation of insoluble strontium chloride (Ref. 1).

(1) *Safety.* The Panel has recommended 0.22 percent sodium fluordie dentifrice as safe for daily use as an anticaries agent (45 FR 20682; March 28, 1980). The formula submitted has 0.44 percent sodium fluoride (Ref. 1). The Panel considers that the increased amount of fluoride gives an increased risk without proven benefit as a tooth desensitizer. Strontium chloride at 10 percent is considered safe by the Panel.

Edetate disodium has chelating properties (Ref. 2). It is considered unsafe by the Panel for use in OTC dental products because chelating properties may cause decalcification of teeth.

(2) *Effectiveness.* Sodium fluoride at 0.22 percent has been recommended for Category III as a tooth desensitizer. Strontium chloride at 10 percent has also been recommended as a Category III tooth desensitizer. There are no data on effectiveness of the combination formulation other than testimonial letters nor are there any data on the effectiveness of edetate disodium as a tooth desensitizer (Ref. 1).

(3) Labeling. The combination product is currently labeled for use by dentists in the office. The Panel takes no position on this use. Labeling the combination for OTC use would result in misbranding.

(4) *Evaluation.* The Panel considers 0.44 percent sodium fluoride unsafe for OTC use. There are no data to support the effectiveness of the combination. The Panel has serious reservations

about OTC use of sodium edetate. The Panel, therefore, recommends that the combination be classified in Category II.

**References**

(1) OTC Volume 080010.

(2) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1113, 1976.

**Category II Labeling**

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of a product are unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

"Gives quick relief that lasts for hours."

"Builds increasing protection against painful sensitivity to cold, heat, sweet, sour, or contact." This claim implies a slow mechanism of action.

The Panel considers that claims which imply a superiority in onset of action, such as "quicker," "more quickly," and "faster," are misleading.

The Panel considers the following terms to be vague and not definitive of the condition for which relief is sought: "anti-irritation," "stops pain," "special," "unaccustomed use," and "alleviates pain."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as noted for specific pharmacotherapeutic groups.

**Category III Active Ingredients**

Citric acid and sodium citrate in poloxamer 407 (pluronic F-127™ gel)
Fluoride preparations (sodium fluoride, sodium monofluorophosphate, and stannous fluoride)
Formaldehyde solution
Potassium nitrate
Strontium chloride

a. *Citric acid and sodium citrate in poloxamer 407 (pluronic F-127™ gel).* The Panel concludes that a combination of citric acid and sodium citrate in poloxamer 407 is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as a tooth desensitizer for the relief of oral discomfort.

(1) *Safety.* After reviewing the submitted data, the Panel finds that there is a marketing history of the use of citric acid, sodium citrate, and poloxamer 407 as individual ingredients but not as a combination product for use as a tooth desensitizer. Citric acid is used in the food industry in the preparation of fruit juice drinks, carbonate beverages, dairy products, and fruit jellies and preserves. Sodium citrate is used in mouthrinses, ice cream, evaporated milk, and in the curing of certain meats. Poloxamer 407 is used in mouthrinses and as a solubilizing and stabilizing agent in food products (Ref. 1). Based on these data the Panel concludes that there is general recognition of safety.

(2) *Effectiveness.* The Panel concludes that the available data are insufficient to establish general recognition of this combination as effective (Ref. 1).

(3) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 2 percent sodium citrate and citric acid in poloxamer 407 in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing tooth desensitizer active ingredients. (See part VI. paragraph B.1. above—Category I labeling.)

(5) *Evaluation.* The Panel concludes that the published data on the combination of citric acid and sodium citrate in poloxamer 407 do establish safety, but they are insufficient to establish effectiveness of the combination as a tooth desensitizer. Data to demonstrate effectiveness of this combination as a tooth desensitizer will be required in accordance with the guidelines set forth elsewhere in this document. (See part II. paragraph E.3. above—Testing guidelines for Category III combination products. See also part VI. paragraph C. below—Data Required for Evaluation.)

**Reference**

(1) OTC Volume 080221.

b. *Fluoride preparations (sodium fluoride, sodium monofluorophosphate, and stannous fluoride).* The Panel concludes that fluoride preparations are safe at the proposed dosages but that there are insufficient data available to permit final classification of their effectiveness for OTC use as tooth desensitizers for the relief of oral discomfort.

(1) *Safety.* The toxicity of fluoride compounds can be attributed to the fluoride ion, which is considered to be protoplasmic poison. Studies of the recorded cases of acute fluoride poisonings indicate that a dose range of 5 to 10 g of sodium fluoride can be considered a lethal dose for a 70-kg man (Refs. 1 and 2).

Much is known of the chronic effects of fluoride because of the widespread use of dietary fluoride in drinking water to provide protection against dental caries. Presently, more than 105 million people in the United States live in areas in which the water supplies contain 0.7 parts per million (ppm) or more fluoride ion, with 94 million of these people receiving water supplemented with additional fluoride to provide a trace level of approximately 1 ppm (Ref. 2). Drinking water having a level of approximately 1 ppm of fluoride will provide a substantial reduction of about 60 percent in the incidence of dental decay without any adverse effect. Dental fluorosis has been reported from daily intake of water with 2 to 10 ppm of fluoride and crippling skeletal fluorosis with levels of 20 to 80 ppm of fluoride in the drinking water (Ref. 3). It should be noted that dental fluorosis occurs only when excessive fluorides are ingested regularly during the period of tooth development.

A number of studies have been conducted, utilizing a variety of testing procedures, to determine the fluoride ingested during toothbrushing with the fluoride-containing dentifrice (Refs. 4 through 9). These studies indicate that, even in children aged 3 to 6 years, the large majority of individuals swallow less than 0.5 g of toothpaste per brushing. The greatest amount swallowed was reported by Hargreaves, Ingram, and Wagg (Ref. 8) as being only slighty over 1 g. If the above information is used when considering a toothpaste formulation containing 0.22 percent sodium fluoride, the amount of fluoride swallowed per average brushing would be 0.25 mg or less. Studies by Ericsson (Ref. 6), Duckworth and Joyston-Bechal (Ref. 10), Barnhart (Ref. 11), and Glass et al. (Ref. 9) all showed the amount swallowed was substantially less than that shown by Hargreaves, Ingram, and Wagg (Refs. 4 and 8). This amount can be considered well below a toxic range.

It is conceivable that a child who regularly swallows excessive amounts of fluoride-containing toothpaste and also consumes fluoridated water could have a total daily fluoride intake in the range that produces dental fluorosis. However, there is a lack of any documentation that dental flurosis has increased significantly following extremely widespread use of fluoride-containing dentifrice for approximately 15 years.

Acute and subacute toxicity studies with sodium monofluorophosphate suggest that the compound on the basis of both milligrams of compound and milligrams of fluorine is less toxic than

sodium fluoride (Refs. 12, 13, and 14). Although the accumulation of fluoride in bone and teeth appears to be similar for sodium monofluorophosphate and sodium fluoride when used at the same fluoride concentration (Ref. 15), studies with radioactive fluoride suggest that the lower toxicity may result from the gradual release of the fluoride ions from the monofluorophosphate (Ref. 16).

Animal feeding studies suggest that the chronic toxicity of sodium monofluorophosphate and sodium fluoride are of the same order and have similar characteristics with the kidney being the most susceptible to pathological change (Ref. 17). Further, the two compounds seem to produce the same degree of mottling in the incisors of albino rats (Ref. 18). When the same quantities of fluoride are given to rats in the form of sodium fluoride, sodium monofluorophosphate , stannous fluoride, and stannous chlorofluoride, similar amounts of fluorine are found in the skeleton (Ref. 19). The monofluorophosphate ion ($PO_3F^=$) also does not appear to pass the placenta to any greater extent than the fluoride ion (Ref. 20).

There is no available information of human toxicity with sodium monofluorophosphate as there is with sodium fluoride. Although acute toxicity of sodium monofluorophosphate in animals is less than that of sodium fluoride, the chronic toxicity is similar. It would, therefore, appear suitable to consider, for human use, that the two compounds have similar toxicity in terms of the fluoride present.

Because stannous fluoride may differ in toxicity from sodium fluoride and sodium monofluorophosphate because of the tin ion, some comments on the acute and chronic toxicity of stannous fluoride may be pertinent. The $LD_{50}$ for mice ingesting stannous fluoride in aqueous solution was found to vary from 169 mg/kg (Ref. 21) to 246 mg/kg (Ref. 22). For rats the $LD_{50}$ was 260 mg/kg (Ref. 21). Levels of stannous fluoride providing up to 18 ppm fluoride in the drinking water or 8 ppm fluoride in the diet for a 140-day period did not inhibit growth or incisor pigmentation in rats. Levels above 9 ppm fluoride in food adversely affected growth and incisor pigmentation and at levels of 150 ppm fluoride some animals died (Ref. 23). Tin from tin salts was reported to have a no-effect level in rats at 22–23 mg/kg and guinea pigs survived on a diet containing 777 ppm tin as tin salt (Ref. 23).

The presence of the stannous ion in stannous fluoride dentifrice formulations may cause some staining of plaque and debris accumulation on the teeth. This has been reported in a number of clinical studies in which an attempt was made to determine the level of staining (Refs. 24, 25, and 26). However, the frequency and intensity of staining with the level of tin present in these formulations does not appear to present any significant problem; therefore, no warning on staining is required for stannous fluoride dentifrice formulations (Ref. 27).

(2) *Effectiveness.* In animal studies, although acute toxicity of sodium monofluorophosphate is less than that of sodium fluoride, the chronic toxicity is similar (Refs. 17, 18, and 20). It would, therefore, appear suitable to consider that the two compounds have similar toxicity for human use. Sodium fluoride, sodium monofluorophosphate, and stannous fluoride have been recommended for Category III as tooth desensitizers. Since the availability of the fluoride ion is similar in all these preparations, it would suggest that the effectiveness data are also related in a similar manner (Ref. 28). The Panel concludes that fluoride-containing dentifrices are safe and effective for OTC use as anticaries agents when marketed in packages containing not more than 260 mg of fluorine, but there are insufficient data to show effectiveness of fluorides as tooth desensitizers at the concentrations permitted in OTC drug products. Effectiveness should be tested for those fluoride compounds that meet the laboratory testing requirements for Category I anticaries fluorides and at the concentrations approved for OTC anticaries use. The laboratory testing requirements recommended by the Panel can be found in the preamble to the proposed monograph on anticaries drug products in the section entitled "Laboratory testing profiles" (45 FR 20677; March 28, 1980).

Kanouse and Ash (Ref. 28) reported favorably on a sodium monofluorophosphate containing dentifrice, but employed a calibrated thermoelectrical device for rating hypersensitivity. Shaprio et al. (Ref. 29) demonstrated reductions in hypersensitivity per individual teeth and per person. Three dentifrices were used, a control, one with sodium monofluorophosphate, and one with strontium chloride. At 4 weeks the reduction with use of the test products was significantly better than the control, but at 8 weeks the difference was no longer apparent. The areas for evaluation were carefully identified and recorded and therefore not blinded. Hernandez et al. (Ref. 30) in a similar study evaluated hypersensitivity at 6 weeks. Hypersensitive areas were not blinded. For a second 6-week period, all three groups (control, sodium monofluorophosphate, and strontium chloride dentifrices) used the control dentifrice. As reported earlier, the net improvement in hypersensitivity for the 12-week control group exceeded the original strontium chloride test group. The Panel felt that additional testing as described below was indicated. (See part VI. paragraph C. below—Data Required for Evaluation.)

In a study designed to evaluate the desensitizing effect of a dentifrice containing 0.76 percent sodium monofluorophosphate, Bolden, Volpe, and King (Ref. 31) included in addition to a nonsodium monofluorophosphate control dentifrice, one with 1.4 percent formalin and one with 0.4 percent stannous fluoride. The sodium monofluorophosphate dentifrice was the superior performer. After 2 weeks the stannous fluoride dentifrice showed the second lowest percent improvement in hypersensitivity. At 4 weeks, it was the lowest of all, including the control. Although a double-blind was established in that neither the examiner nor the patient was aware of the dentifirce assignment, all evaluations were done "in exactly the same anatomical tooth areas that had been previously evaluated" for the baseline data. This procedure may have introduced a potential bias favoring reduction in sensitivity from the use of the "blinded" dentifrices. The Panel felt the areas for evaluation should also be blinded. Hazen, Volpe, and King (Ref. 32), in a duplicate study using the same agents, found stannous fluoride second only to the dentifrice with sodium monofluorophosphate in its ability to reduce hypersensitivity in teeth. The evaluation of hypersensitive areas was not blinded.

Miller et al. (Ref. 33) in a double-blind crossover study reported improvement in hypersensitivity in 20 of 23 patients with the use of a water-free stannous fluoride-containing gel. Hypersensitive areas were not blinded, nor were the specific measures used to evaluate changes in sensitivity described. The Panel felt that additional testing as described below was indicated. (See part VI. paragraph C. below—Data Required for Evaluation.)

(4) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 0.22 percent sodium fluoride, 0.76 percent sodium monofluorophosphate, or 0.4 percent stannous fluoride in a suitable dentifrice formulation.

(5) *Labeling.* The Panel recommends the Category I labeling for products containing tooth desensitizer active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

In addition, fluoride-containing dentifrices should not contain more than 260 mg total fluorine.

(6) *Evaluation.* The Panel concludes that OTC Category I anticaries fluoride dentifrices are Category III with respect to claims as tooth desensitizing agents. The Panel concludes that fluoride dentifrices are safe at the proposed dosage, but there is insufficient evidence to establish effectiveness as tooth desensitizing agents. Data to demonstrate effectiveness as a tooth desensitizer will be required in accordance with the guidelines set forth below. (See part VI. paragraph C. below—Data Required for Evaluation.)

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c. *Formaldehyde solution.* The Panel concludes that 1.4 percent (w/w) formaldehyde solution is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as a tooth desensitizer for the relief of oral discomfort.

(1) *Safety.* Clinical use and marketing experience have confirmed that 1.4 percent (w/w) of formaldehyde solution is safe for OTC use.

Formaldehyde solution is an aqueous solution containing approximately 40 percent weight to volume of formaldehyde gas with methanol added as a preservative. Formaldehyde solution is clear and colorless and has a pungent odor. The solution is incompatible with oxidizing agents and with alkali (Ref. 1).

Contact with formaldehyde solutions may lead to dermatitis producing reddening, inflammation, and necrosis if applied repeatedly by allergic or sensitive individuals (Refs. 1 and 2). A manufacturer of a 1.4-percent (w/w) formaldehyde solution-containing dentifrice reported a low incidence of consumer complaints of mouth reactions or gingival injuries from the use of this product (Ref. 3).

(2) *Effectiveness.* Although formaldehyde solution has been used for the relief of pain due to hypersensitive teeth, its effectiveness in a dentifrice for desensitizing has not been conclusive. In one study, 20 patients were selected on the basis of cervical hypersensitivity and evaluated by application of mechanical and thermal (heat and cold) stimuli (Ref. 4). Subjects were advised to brush with the dentifrice at least once daily or as many times a day as they did prior to use of the dentifrice. This study was of controlled, crossover design. At the end of a 30-day treatment period the placebo group was switched to the treatment dentifrice, and the original treatment group was continued for an additional 30 days. The conclusion was that there was no significant alteration

of cervical hypersensitivity to mechanical or thermal stimuli after use of this product for 30 or 60 days.

In another study 72 adults, all having a history of dental hypersensitivity, were selected for treatment of chronic periodontitis (Ref. 5). Forty-seven patients were instructed to brush after each meal with a desensitizing tooth paste. Twenty-four patients were placed in a placebo group using a control dentrifice. The patients used one of the dentifrices for 5 weeks during which time they received periodontal therapy (root planing and gingivectomy). This was a double-blind, subjective evaluation with no statistical analysis. The conclusion was that the product may be of some value for patients undergoing periodontal therapy.

When a formaldehyde solution-containing dentifrice was compared with one containing sodium monofluorophosphate, the desensitizing effectiveness of 1.4 percent formaldehyde was not as great as that of the sodium monofluorophosphate dentifrice (23.5 percent vs. 29.2 percent) after 2 weeks of treatment, but was slightly better than the control (50.6 percent vs. 46.0 percent) after 4 weeks of treatment (Ref. 6). These differences are not statistically significant. Another study compared sodium monofluorophosphate, a control dentifrice without sodium monofluorophosphate, and a 1.4 percent formaldehyde dentifrice. At the end of 4 weeks the control dentifrice without sodium monofluorophosphate provided 38 percent reduction of sensitivity, and the formaldehyde-containing dentifrice provided a 33.8-percent reduction. These reductions were not statistically different from each other (Ref. 7).

Several other studies gave ambiguous results (Refs. 8 through 11). Although the use of a formaldehyde-containing dentifrice appeared to give favorable results in some instances, basic defects in experimental design or lack of statistical significance left doubts concerning the effectiveness of the product.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 1.4 percent (w/w) formaldehyde solution in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling for tooth desensitizer active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there is insufficient information to establish the effectiveness of 1.4 percent (w/w) formaldehyde solution in a suitable dentifrice formulation as a tooth desensitizer. Data to demonstrate effectiveness as a tooth desensitizer will be required in accordance with the guidelines set forth below. (See part VI. paragraph C. below—Data Required for Evaluation.)

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d. *Potassium nitrate.* The Panel concludes that 5 percent potassium nitrate is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as a tooth desensitizer for the relief of oral discomfort.

(1) *Safety.* Nitrates are components of the normal environment. Soil bacteria are principally responsible for their presence, although compounds of nitrogen, during transport in the air, can be oxidized to nitrates. Large deposits of nitrate salts formed in this way exist in various locations on the earth.

Nitrates in the soil are the primary source of fixed nitrogen for green plants. A second source is ammonia in the soil, either from natural (bacterial action on dead plant or animal matter) or synthetic (applied fertilizer) sources. Nitrates are absorbed and may accumulate in plants at high levels, especially if the soil is rich in nitrates. Some vegetables, notably lettuce, beets, celery, radishes, and spinach contain substantial quantities of nitrates. An estimated average per capita daily ingestion of nitrate in the United States is 86 mg. This comes principally from vegetables but there is a great variation in intake depending upon the type and quantity of the vegetables consumed and the condition of the soil in which the vegetables were grown. Until elimination, cheifly via the urine, nitrate is recycled by secretion in the saliva. The nitrate-to-nitrite conversion does not take place in the 5-percent dentifrice product which was submitted to the Panel (Ref. 1). No known toxic effects are produced in man in doses of 1 to 1.5 g potassium nitrate. In light of the estimated dietary intake of nitrates (86 mg) and the relatively small amount (30 mg) available for ingestion from the use of a toothpaste, the Panel concludes that no toxicological hazard exists from use of a dentifrice with potassium nitrate at the 5-percent level.

(2) *Effectiveness.* Two published studies and two unpublished studies are reviewed below (Refs. 1 through 4). Among these four studies only limited data are presented on the 5-percent potassium nitrate toothpaste. In some instances the findings are conflicting and are always based on very small samples of persons and teeth. An 8.5-percent potassium nitrate dental prophylaxis paste available OTC has been promoted to the dental profession for office use since 1974 (Ref. 1). The Panel agreed that the marketing experience data concerning this product could not be substituted for marketing experience with an OTC dentifrice intended for use at home. The Hodosh study (Ref. 2) described this positive effect of potassium nitrate in solutions of 15, 10, 5, 2, and 1 percent when painted on hypersensitive teeth. A 10-percent potassium nitrate paste for office use was also reported. Only 35 patients used the home dentifrice (10 percent potassium nitrate by weight), but positive results were reported. However, no controls were used, no system of evaluation was described, and no statistical analysis was included.

In a report of Stark et al. (Ref. 3), on a new device for testing sensitivity, a potassium nitrate dentifrice was used successfully by 10 patients. The primary purpose of this study was to compare findings of a new electric pulp test against conventional pulp testers. The concentration of potassium nitrate in the dentifrice was not stated. Additional

study of the data reported by Stark et al. (Ref. 3) disclosed that for one group (five persons, but only three with hypersensitive teeth) a significant reduction in hypersensitivity was found immediately after application of the potassium nitrate (5-percent solution). This is contrary to Starks' published findings (Ref. 3), where there was little or no immediate reduction in sensitivity. Seven days later, sensitivity was rated again and a paste containing 5 percent potassium nitrate in kaolin and glycerin paste was burnished by the dentist against the cervical area of the teeth. Reduction in hypersensitivity was maintained at each assessment. Normal oral hygiene including brushing with a dentifrice without a desensitizing agent was followed throughout the study (Ref. 3).

In a second unpublished study potassium nitrate at 5 and 10 percent in home-use dentifrices was compared with a single application of sodium fluoride, 33⅓ percent, in a kaolin and glycerin burnishing paste (Ref. 1). The study groups were composed of 7, 14, and 6 persons, respectively. Immediate reduction in sensitivity was significant with the burnished fluoride paste but not with potassium nitrate toothpastes. Significant reduction was reported at 1 week for the 10-percent potassium nitrate paste and at 2 weeks for both the 5-percent and 10-percent pastes.

Three additional unpublished studies, one evaluating a test procedure and two others presenting data on potassium nitrate, were submitted to the Panel for review (Ref. 4). The first compares the pulp stethoscope with cold air as a procedure for evaluating hypersensitivity. The data suggest that the two test procedures are assessing the various levels of sensitivity in a comparable manner. The two other studies present data on the use of potassium nitrate in a desensitizer dentifrice. The findings indicate that the potassium nitrate dentifrice may be effective in reducing sensitivity, but the evidence is not convincing. The test groups were somewhat small in number and, in several, the levels of initial hypersensitivity were very low.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 5 percent potassium nitrate in a suitable dentifrice dosage form.

(4) *Labeling.* The Panel recommends the Category I labeling for tooth densensitizer active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that 5 percent potassium nitrate is safe but that there are insufficient data to establish effectiveness of 5 percent potassium nitrate in a suitable dentrifice formulation as a tooth densensitizer. Although the product is available without a prescription, marketing experience has been limited to use by professionals in the dental office. Data to demonstrate effectiveness as a tooth densensitizer will be required in accordancewith the guidelines set forth below. (See part VI. paragraph C. below—Data Required for Evaluation.)

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e. *Strontium chloride.* The Panel concludes that 10 percent strontium chloride is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as a tooth desensitizer for the relief of oral discomfort.

(1) *Safety.* Animal studies have clearly shown that some strontium compounds are tolerated in what could be considered large amounts (Refs. 1 through 4). There is general agreement that strontium chloride hexahydrate is no more and may even be less toxic than calcium (Refs. 1, 3, 10, and 11). Reports on strontium chloride hexahydrate are limited, but are consistent in that safety does not appear to be a problem (Refs. 2 and 3). Industry-sponsored studies of strontium chloride hexahydrate at 10 percent by weight in a dentifrice produced no measurable toxic reactions (Ref. 5).

The metabolism of strontium resembles very closely that of calcium, especially with regard to developing bone and teeth (Ref. 6). Interest in its behavior as a radioactive isotope, strontium 90, heightened in recent years since it is a constituent of the fallout from atomic weapon testing (Refs. 6 and 7). The consequent hazard from the accumulation of the isotope in bones and teeth drew much attention.

One review of the toxicity of strontium states that no threshold values for human toxicity have been reported by any official agency in the United States (Ref. 7). Strontium chloride hexahydrate, present at 10 percent by weight in a toothpaste, has been marketed for 12 years with no report of adverse reactions (Ref. 5). Published clinical studies contain no reports of adverse reactions (Refs. 10 through 13). The Panel agreed that strontium chloride as the hexahydrate appears to be safe for OTC use in a dentifrice at a concentration of 10 percent.

(2) *Effectiveness.* The Panel found that the reported findings from various clinical trials of dentifrices containing strontium chloride were both conflicting and inconclusive. The required time for reducing sensitivity has been variously reported at 3 days and 20 days by Pusso-Carrasco (Ref. 11), at 6 weeks by Hernandez et al. (Ref. 14), and at 4- and 8-week periods by Shapiro et al. (Ref. 15).

Hernandez et al. (Ref. 14), after a 6-week evaluation, placed the two test groups (sodium monoflurophosphate and strontium chloride) on the control dentifrice and continued the original control group on the control dentifrice for an additional 6 weeks. Both test groups lost some of the improvement in hypersensitivity gained during the first 6 weeks. The control group improved remarkably during the second 6-week period to a level slightly better than the test group formerly using the strontium chloride dentifrice.

An unpublished study conducted at the Osaka University Dental School, Osaka, Japan (Ref. 16), was submitted to the Panel for review. A unique and surprising result of this study was very low response to the placebo product.

In a well-controlled, double-blinded clinical trial reported by Graf (Ref. 17), both the test group and the control group showed measurable reduction in hypersensitivity at 4, 8, and 12 weeks. The difference between the test and control groups was not statistically significant, however. In a second attempt, Graf (Ref. 17) found similar results at 3 months and not until 6 months could a statistical significance be established between test and control group reductions in hypersensitivity. The lack of early, consistent, favorable, and statistically significant results from clinical studies left the Panel with many doubts about the effectiveness of strontum chloride as an agent for the reduction of dental hypersensitivity.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 10 percent strontium chloride in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling for tooth desensitizer active igredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that 10 percent strontium chloride is safe but that there are insufficient data to establish the effectiveness of 10 percent strontium chloride in a suitable dentifrice formulation as a tooth desensitizer. Data to demonstrate effectiveness as a tooth desensitizer will be required in accordance with the guidelines set forth below. (See part VI. paragraph C. below—Data Required for Evaluation.)

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(16) OTC Volume 080257.

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**Category III Labeling**

None.

*C. Data Required for Evaluation.*

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *General principles in the design of an experimental protocol for testing tooth desensitizers.* Three independent investigations will be required. An academic setting for the studies seems most appropriate since most private offices and clinics would have neither the facilities nor the volume of patients necessary for the projects.

Monitoring of the studies should be as complete as possible. Placebo samples must be indistinguishable from test samples with regard to taste, consistency, and appearance. The abrasive in the test product should be the same as that used in the placebo. Both test and placebo samples should be assigned random numbers and the code should not be broken until the completion of the study. Data may be evaluated by sequential analysis of paired test and placebo trials. This seems to be the most efficient methodology, but other recognized and accepted study designs and statistical analyses are acceptable. The two criteria for change in sensitivity described later must be met for an active ingredient to be considered effective.

2. *Selection of patients.* At an initial screening, selected patients should complain of hypersensitive teeth (or tooth) limited to either or both of the following types: (1) Postperiodontal surgery (6 weeks minimum) (Type I), and (2) cervical erosion, abrasion, or exposed dentin resulting from gingival recession (Type II).

All other types of hypersensitivity should be rejected.

Each of the investigations should include persons with the same type of sensitivity (as described above). Among the three investigations, at least one must be on persons with Type I sensitivity.

Persons selected for test and placebo trials should be of the same sex and reasonably similar in age, in number of hypersensitive teeth, and in the mean sensitivity score. Appropriate release forms should be completed, and institutional approval for human experimentation must be given.

Teeth which may be included in the study are the incisors, canines, and premolars in both arches.

3. *Study method.* In the case of postperiodontal surgery, Type I sensitivity, rating the sensitivity of an interproximal space of two adjacent teeth is not acceptable. The facial surface of the individual tooth is the assessment unit.

For persons with Type II sensitivity, sensitivity will be rated on the facial surface of all teeth present in both jaws except those teeth with pulpitis, cracked enamel, or fillings on some part of the facial surface. Rating all teeth will additionally blind the examiner and the study person. Ratings will be done on individual teeth isolated from adjacent teeth mesially and distally by the examiners' fingers, cotton rolls, or some other appropriate device.

The use of tactile stimulation as a method of evaluating tooth hypersensitivity has been traditional. It is a very familiar clinical procedure to most practicing dentists. Difficulties have been encountered by many researchers in establishing a standardized tactile procedure and in assessing the degree of standardization either among examiners at a point in time or within the same examiner over time. Therefore, other assessment procedures have been sought which have more obvious and measurable levels of reliability. The Panel encourages the further development and use of these improved procedures. The use of tactile stimulation for the evaluation of tooth hypersensitivity is acceptable but is not encouraged.

The sensitivity rating will be the subjective response of the study person to a standardized thermal stimulus according to the following scale:

0=no significant discomfort, aware of stimulus
1=discomfort but no severe pain
2=severe pain during application of stimulus
3=severe pain during and continuing after application of stimulus

One of the following standardized stimulus mechanisms may be used:

(1) 1 second or less of cold air from the air syringe making certain that the time and the air temperature and pressure are standardized for each rating.

(2) 0.2 mL of ice water on an isolated surface making certain that the time and temperature are standardized for each rating.

(3) Selected levels applied by the thermoelectric stimulator described by Smith and Ash (Ref. 1).

(4) Electrical stimulation with microcurrents at variable levels.

(5) Tactile stimulation by the dental explorer for a stated time interval and at a standard pressure.

The reduction in hypersensitivity will be measured by comparing the mean sensitivity scores at the initiation of the investigation with the mean scores at the various test intervals.

Mean sensitivity score-*initial*=Summation of 1, 2, 3 ratings divided by number of teeth so rated (exclude 0-rated teeth).

Mean sensitivity score-*test interval*=Summation of all ratings for teeth included in initial mean score divided by number of teeth scored (include 0-rated teeth).

Following the initial sensitivity ratings, evaluation for sensitivity should be completed at 2-week, 4-week, and 8-week intervals. Additional evaluations at 4 and 6 months, although not recommended by the Panel, are optional.

4. *Interpretation of data.* If sequential trial charts are used, they will be completed at the end of the 8-week trial without a break in the coding during the period. (Those persons on placebo who claim no relief of pain should be treated for hypersensitivity following the test period.) Assessment of paired sample persons will be made at the 2-, 4-, and 8-week periods.

In determining the boundaries for the analysis chart, the probabilities of errors should range from 5 to 10 percent. Paired sample persons will be entered on the analysis chart only when the active ingredient has demonstrated a reduction of 33 percent or greater in the initial mean sensitivity score. A favorable placement on the chart will be made when the active ingredient shows a 50-percent greater reduction in the mean sensitivity score than the placebo reduction.

Regardless of the study design or the statistical analysis employed, to be considered effective, the active ingredient must demonstrate the above-stated requirements, i.e., 33-percent or greater reduction in the initial mean sensitivity score and a 50-percent greater reduction than the placebo reduction.

*Example* first paired sample persons:

| | Mean sensitivity scores | |
|---|---|---|
| | Active | Placebo |
| Initial Mean | 2.5 | 2.4 |
| 2 Week Mean | 1.5 | 2.0 |
| Percent Reduction | 40 | 17 |

A 40-percent reduction is greater than 33 percent; therefore, the paired sample is eligible for the analysis chart. A favorable placement on the chart is indicated since the 40-percent reduction for the active is more than 50 percent greater than the 17-percent reduction for the placebo.

The Panel has agreed that 3 years after the publication of the proposed rules is an adequate time period for completion and submission of data for these studies.

**Reference**

(1) Smith, B. A., and M. M. Ash, "Evaluation of a Desensitizing Dentifrice," *Journal of the American Dental Association*, 68:639–647, 1964.

**List of Subjects in 21 CFR Part 354**

Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding new Part 354, to read as follows:

## PART 354—DRUG PRODUCTS FOR THE RELIEF OF ORAL DISCOMFORT FOR OVER-THE-COUNTER HUMAN USE

**Subpart A—General Provisions**

Sec.



**Subpart B—Active Ingredients**



**Subpart C—[Reserved]**

**Subpart D—Labeling**



**Authority:** Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

### Subpart A—General Provisions

**§ 354.1 Scope.**

(a) An over-the-counter drug product for the relief of oral discomfort in a form suitable for topical oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

**§ 354.3 Definitions.**

As used in this part:

(a) *Agent for the relief of oral discomfort.* An ingredient which when applied topically has direct or indirect capability to relieve oral discomfort. This category of drugs includes oral mucosal analgesics, tooth desensitizers, oral mucosal protectants, and agents for the relief of toothache.

(b) *Agent for the relief of toothache.* An ingredient used for the temporary relief of pain arising as a result of an open tooth cavity.

(c) *Oral mucosal analgesic.* An ingredient used in dental care drug products for topical application in the oral cavity to provide temporary relief of oral discomfort by an anesthetic or analgesic effect.

(d) *Oral mucosal protectant.* An ingredient which is a pharmacologically inert substance which forms an adherent, continuous, flexible, or semirigid coating when applied to the oral mucous membranes. The coating protects the irritated area from further irritation due to the activity of oral structures.

(e) *Tooth desensitizer.* An ingredient which acts on the dentin to block perception of those stimuli which are usually not perceived by normal subjects but which are perceived by patients with dental hypersensitivity.

### Subpart B—Active Ingredients.

**§ 354.10 Agents for the relief of toothache.**

The active ingredient of the product may consist of the following when used within the dosage limit established: Eugenol 85 to 87 percent.

**§ 354.12 Oral mucosal analgesics.**

The active ingredients of the product may consist of any of the following

when used within the dosage limits established for each ingredient:

(a) Benzocaine 5 to 20 percent.

(b) Butacaine sulfate 4 percent.

(c) Phenol preparations (phenol and phenolate sodium) 0.25 to 1.5 percent.

**§ 354.14 Oral mucosal protectants.**

The active ingredient of the product may consist of any of the following when used within the dosage limits established for each ingredient:

*Benzoin preparations.* (a) Compound benzoin tincture, USP XIX.

(b) Benzoin tincture, USP XV.

**§ 354.16 Tooth desensitizers. [Reserved]**

**§ 354.18 Package size limitations.**

(a) Products containing butacaine sulfate identified in § 354.12(b) should be packaged in single-use units to contain no more than 30 milligrams each with no more than six units per package.

(b) Products containing benzoin preparations identified in § 354.14 should be packaged in well-closed containers in a quantity of 30 milliliters or less.

**§ 354.20 Permitted combinations of active ingredients.**

(a) Any single oral mucosal protectant active ingredient identified in § 354.14 may be combined with any single oral mucosal analgesic active ingredient identified in § 354.12.

(b) Any single oral mucosal protectant active ingredient identified in § 354.14 may be combined with any generally recognized safe and effective oral antiseptic.

(c) Any single oral mucosal analgesic active ingredient identified in § 354.12 may be combined with any generally recognized safe and effective oral antiseptic.

(d) Any single oral mucosal protectant active ingredient identified in § 354.14 and any single oral mucosal analgesic active ingredient identified in § 354.12 may be combined with any generally recognized safe and effective oral antiseptic.

(e) Any single oral mucosal analgesic active ingredient identified in § 354.12 may be combined with any generally recognized safe and effective denture adhesive.

## Subpart C [Reserved]

## Subpart D—Labeling

**§ 354.50 Labeling of agents for the relief of toothache drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "agent for the relief of toothache."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "for the temporary relief of throbbing, persistent toothache due to a cavity until a dentist can be seen."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 354.10.* (i) "Use only in teeth with persistent, throbbing pain."

(ii) "Not to be used for a period exceeding 7 days."

(iii) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(iv) "Do not swallow."

(v) "Do not exceed recommended dosage."

(vi) "Children under 12 years of age should be supervised in the use of this product."

(vii) "A dentist must be seen as soon as possible whether or not the paid is relieved."

(viii) "Toothaches and open cavities indicate serious problems which need prompt attention by a dentist."

(2) *For products containing eugenol identified in § 354.10.* "Do not use if you are allergic to eugenol."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": "Rinse the tooth with water to remove any food particles from the cavity. Moisten a cotton pledget with 1 or 2 drops of medication and place in the cavity for approximately 1 minute. Avoid touching tissues other than the tooth cavity. Apply the dose not more than four times daily or as directed by a dentist or physician. Children 2 to 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician."

**§ 354.55 Labeling of oral mucosal analgesic drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral mucosal analgesic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following:

(1) *For products containing any ingredient identified in § 354.12.* (i) "For the temporary relief of pain due to minor irritation or injury of soft tissue of the mouth."

(ii) "For the temporary relief of pain due to minor dental procedures."

(iii) "For the temporary relief of pain due to minor irritation of soft tissues caused by dentures or orthodontic appliances."

(iv) "For the temporary relief of pain due to recurring canker sores when the condition has been previously diagnosed by a dentist."

(2) *For products containing benzocaine identified in § 354.12(a) or phenol identified in § 354.12(c) when used as oral mucosal analgesics for teething pain.* "For the temporary relief of sore gums due to teething in infants and children 4 months of age and older."

(3) *For products containing any ingredient identified in § 354.12 when used in denture adhesive products.* "For the temporary relief of pain or discomfort of oral tissues due to dentures."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 354.12.* (i) "Not to be used for a period exceeding 7 days."

(ii) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(iii) "Do not swallow."

(iv) "Do not exceed recommended dosage."

(2) *For products containing any ingredient identified in §§ 354.12 (a) and (c).* "Children under 12 years of age should be supervised in the use of this product."

(3) *For products containing "caine" derivatives identified in §§ 354.12 (a) and (b).* "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(4) *For products containing butacaine sulfate identified in § 354.12(b).* (i) "Do not use in children under 12 years of age unless recommended by a dentist or physician."

(ii) "Do not use more than one unit at a time."

(iii) "Do not repeat except after 3 hours."

(iv) "Do not exceed 3 doses daily."

(5) *For products labeled with the indication identified in § 354.55(b)(2).* "Fever and nasal congestion are not symptoms of teething and may indicate

the presence of infection. If these symptoms persist, consult your physician."

(6) *For products containing any ingredient identified in § 354.12 when used in denture adhesive products.* "See your dentist as soon as possible."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *For products containing benzocaine identified in § 354.12(a).* "Apply to the affected area not more than four times daily or as directed by a dentist or physician. For infants under 4 months of age there is no recommended dosage or treatment except under the advice and supervision of a dentist or physician."

(2) *For products containing butacaine sulfate identified in § 354.12(b).* "Apply to the affected area. Do not use more than one unit at a time (each unit to contain no more than 30 milligrams butacaine sulfate). Do not apply more often than every 3 hours. Do not exceed three applications (90 milligrams) daily. Children under 12 years of age should not use this product except under the advice and supervision of a dentist or physician."

(3) *For products containing phenol identified in § 354.12(c) when used as teething preparations.* "Apply to the affected area not more than six times daily. For infants under 4 months of age, there is no recommended dosage except under the advice and supervision of a dentist or physician." For infants and children 4 months to under 12 years of age, dosage should not exceed 300 milligrams of phenol per day.

(4) *For products containing phenol identified in § 354.12(c) when used as a dental rinse.* "Rinse the affected area not more than six times daily. For children under 6 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician." For adults and children 12 years of age and older, dosage should not exceed 600 milligrams of phenol per day. For children 6 to under 12 years of age, dosage should not exceed 300 milligrams of phenol per day.

(5) *For products containing any ingredient identified in § 354.12 when used in denture adhesive products.* "Apply on area of denture that comes in contact with sore gums."

**§ 354.60 Labeling of oral mucosal protectant drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral mucosal protectant."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following:

(1) "Forms a coating over a wound."

(2) "Protects against further irritation."

(3) "For temporary use to protect wounds caused by minor irritations or injury."

(4) "For protecting recurring canker sores when the condition has been previously diagnosed by a dentist."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) "Not to be used for a period exceeding 7 days."

(2) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(3) "Do not swallow."

(4) "Do not exceed recommended dosage."

(5) "Children under 12 years of age should be supervised in the use of this product."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": "For adults and children 6 months of age and older: Dry the affected area, saturate a cotton applicator with medication, and apply undiluted to the affected area not more often than every 2 hours. For children under 6 months of age, there is no recommended dosage except under the advice and supervision of a dentist or physician."

**§ 354.65 Labeling of tooth desensitizer drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "tooth desensitizer."

(b) *Indications.* The labeling of the product contains a statement under the heading "Indications" that is limited to the phrase "to aid in the reduction of painful sensitivity of the teeth to cold, heat, acids, sweets, or contact."

(c) *Warnings.* The labeling of the product contains the following warinings under the heading "Warnings":

(1) "Do not continue use beyond 2 weeks except under supervision of a dentist."

(2) "Do not swallow."

(3) "Children under 12 years of age should be supervised in the use of this product."

(4) "Sensitive teeth may indicate a serious problem which needs prompt care by a dentist."

(5) "See your dentist as soon as possible whether or not relief is obtained."

(6) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(7) "Do not exceed recommended dosage."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": "Apply with a toothbrush at least once a day or as recommended by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician."

Interested persons may, on or before August 23, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before September 22, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 31, 1982.

**Mark Novitch,**

*Acting Commissioner of Food and Drugs.*

Dated: May 13, 1982.

**Richard S. Schweiker,**

*Secretary of Health and Human Services.*

[FR Doc. 82–13917 Filed 5–24–82; 8:45 am]

BILLING CODE 4160–01–M

21 CFR Part 356

[Docket No. 81N-0033]

## Oral Health Care Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

**AGENCY:** Food and Drug Administration.

**ACTION:** Advance notice of proposed rulemaking.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) oral health care drug products (products for use in the mouth and throat) are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Oral Cavity Drug Products and is part of the ongoing review of OTC drug products conducted by FDA

**DATES:** Written comments by August 23, 1982, and reply comments by September 22, 1982.

**ADDRESS:** Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** William E. Gilvertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

**SUPPLEMENTARY INFORMATION:** In accordance with Part 330 (21 CFR Part 330), FDA received on December 14, 1979 a report on OTC oral health care drug products from the Advisory Review Panel on OTC Oral Cavity Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed order containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC oral health care drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC oral health care drug products as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency notes that the Panel was charged to review the use of oral health care products as drugs but recognizes that many claims for these products historically have been considered cosmetic in nature. The Panel made specific recommendations on the cosmetic use of oral health care products, e.g., products containing pharmacologically active ingredients should not be used to achieve a cosmetic effect such as reduction of mouth odors. Also, there are numerous instances in which the Panel refers to the drug or cosmetic status of certain ingredients and claims. The Panel's recommendations and conclusions, if fully implemented, would result in extensive changes in the marketing of these products. As with other Oral Cavity Panel recommendations, the agency is deferring its decision with regard to the "drug versus cosmetic" status of OTC oral health care products until publication of the tentative final rule. This issue is important and requires careful study. The agency points out that is has previously discussed the "drug versus cosmetic" status of soaps containing antimicorbial ingredints in the rulemaking proceeding to establish a monograph for OTC topical antimicrobial drug products (39 FR 33103 and 43 FR 1212) and invites specific comments on this subject with regard to the oral health care products discussed in this document.

The agency's position on OTC oral health care drug products will be stated initially when the tentative final monograph is published in the **Federal Register** as a proposed regulation. In the preamble to the tentative final monograph, the agency also will announce its initial determination whether the monograph is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the tentative final monograph is published. At that time FDA also will consider whether the monograph has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC oral health care drug products. Types of impact may include, but are not limited to, the following: increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC oral health care drug products should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC oral health care drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after June 24, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph had been established.

Accordingly this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the result of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under *Cutler,* FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug produ cts that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug products that are subject to the monogrph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially intruduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monogroph regardless of the date the product was initally intruduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC oral cavity drug products was issued in the **Federal Register** of July 20, 1973 (38 FR 19444). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure of any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other then an 'active ingredient.' ")

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of those products:

Lawrence Cohen, Ph. D., M.D., D.D.S., Chairman
John Adriani, M.D. (appointed June 1974)
Roy C. Darlington, Ph. D.
Martin J. Goldberg, D.D.S.
Valerie Hurst, Ph. D.
Walter E. Loch, M.D.
Jeanne C. Sinkford, D.D.S. (resigned June 1974)

Arthur N. Bahn, Ph. D. (resigned July 1977 to accept a sabbatical appointment to the University of Utrecht for the period August 1977 to September 1978. He was reappointed to the Panel in December 1978. The vacancy created by his resignation was not filled.)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Mary Plaska served as the consumer liaison until she resigned in June 1977, and was followed by Sandra Zimmerman. Both were nominated by an ad hoc group of consumer organizations. Christopher H. Costello, Ph. D. (nominated by the Proprietary Association), served as an industry liaison throughout the Panel's deliberations. Kenneth W. Herrman, Ph. D. (nominated by the Cosmetic, Toiletry, and Fragrance Association), served as an industry liaison until February 1975, followed by Joseph Ambrozaitis, Ph. D., who served until June 1977, followed by Barry Gibberman, Ph. D., who served until February 1978.

Six nonvoting consultants provided assistance to the Panel:

William Bowen, D.D.S.
Neal W. Chilton, D.D.S., M.P.H.
Ralph B. D'Agostino, Ph. D.
Frank B. Engley, Ph. D.
Gordon Pledger, Ph. D.
Sigmund S. Socransky, Ph. D.

The following FDA employees assisted the Panel: John R. Carr, D.D.S., served as Executive Secretary. John T. McElroy, J.D., served as Panel Administrator. Melvin Lessing, R.Ph., M.S., served as Drug Information Analyst until October 1977, followed by Cynthia Rutten, R.Ph., until December 1978, followed by Chester Trybus.

The Panel was first convened on February 26, 1974, in an organizational meeting. Working meetings were held on April 23, June 13 and 14, September 5 and 6, November 7 and 8, December 11 and 12, 1974; February 6 and 7, March 4 and 5, April 24 and 25, July 9 and 10, September 9 and 10, October 16 and 17, December 11 and 12, 1975; February 19 and 20, March 10 and 11, May 6 and 7, July 7 and 8, September 30 and October 1, December 9 and 10, 1976; February 23 and 24, April 12 and 13, June 9 and 10, July 20 and 21, 1977; June 6 and 7, October 17 and 18, 1978; January 4 and 5, August 14, and December 12, 13, and 14, 1979.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above).

The following individuals were given an opportunity to appear before the Panel, either at their own request or at the request of the Panel, to express their views on oral health care drug products:

Joseph F. Alexander, Ph. D.
Russell J. L. Allen, Ph. D.
Hazen J. Barron, D.D.S., Ph. D.
Robert Blank, Ph. D.
James F. Bosma, M.D.
William Bowen, D.D.S.
H. Alexander Bradford, M.S.
William Briner, Ph. D.
Richard C. Brogle, Ph. D.
Lewis P. Cancro, Ph. D.
Steven Carson, Ph. D.
Neal W. Chilton, D.D.S., M.P.H.
Sebastian G. Ciancio, D.D.S.
Joseph Clark, Ph. D.
John M. Clayton, Ph. D.
Eugene A. Conrad, Ph. D.
William E. Cooley, Ph. D.
Ralph B. D'Agostino, Ph. D.
Salvatore J. DeSalva, Ph. D.
Dennis G. Economy, M.D.
Jane F. Emele, Ph. D.
Frank B. Engley, Ph. D.
Raymond C. Erickson, Ph. D.
Malcolm H. Fine, M.D.
Arthur Flanagan, M.D.
Thomas Gerding, Ph. D.
William Gold, Ph. D.
George S. Goldstein, M.D.
Jack Goodman, Ph. D.
George F. Hoffnagle, Sc. D.

F. Allen Hofmann, D.D.S.
L. Honkomp, M.D.
Dennis Huston
Eugene R. Jolly, M.D., Ph. D.
Joseph L. Kanig, Ph. D.
J. Vernon Knight, M.D.
Gerald Kowitz, D.D.S.
Ralph R. Lobene, D.D.S., M.S.
Jean Lockhart, M.D.
Harold Loe, D.D.S.
Walter J. Loesche, D.M.D., Ph. D.
H. J. Lutz
Irwin Mandel, D.D.S.
John H. Manhold, D.M.D., M.A.
Gerald McCowen
Thomas F. McNamara, Ph. D.
Raymond A. Nelson
James W. Newberne, D.M.D.
M. W. Noall, Ph. D.
Bernard L. Oser, Ph. D.
William J. Phelan, M.D.
Gary Pitts, Ph. D.
Gordon W. Pledger, Ph. D.
Phyllis E. Riley, Ph. D.
Francis J. C. Roe, D.M., F.R.C. Path.
George W. Rogers, M.D.
Norton Ross, D.D.S., M.A.
Eugene R. Rubacky, Ph. D.
Arthur J. Saffir, D.M.D., Ph. D.
Max Samter, M.D.
Irving R. Schmolka, Ph. D.
Gordon Schrotenboer, Ph. D.
H. A. Shelanski, M.D.
Morris V. Shelanski, M.D.
Sigmund S. Socransky, D.D.S.
Robert Stafford
Anthony Volpe, D.D.S., M.S.
Murray Werner, M.D.
C. R. Willis, Ph. D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through December 14, 1979, in arriving at its conclusions and recommendations.

The charge to the Panel required the review of OTC "oral cavity" drugs. However, the Panel decided to adopt the term "oral health care" when referring to products that are used for the temporary relief of symptoms due to minor irritations, inflammations, and other lesions on the mucous membranes of the mouth and throat. The Panel concluded that "oral health care" would be a more appropriate term to describe the function of these products to the lay public. (See part II. paragraph B.1. below—Introduction, and part II. paragraph B.2. below—Oral health care.) Accordingly, these products are referred to as "oral health care drug products" throughout this document.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC oral health care drug products with respect to the following three categories:

**Category I**

Conditions under which OTC oral health care drug products are generally recognized as safe and effective and are not misbranded.

**Category II**

Conditions under which OTC oral health care drug products are not generally recognized as safe and effective or are misbranded.

**Category III**

Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 25 active ingredients for use as oral health care agents. The Panel placed 9 ingredients in Category I, 10 ingredients in Category II, and 3 ingredients in Category III for analgesic/anesthetic use. The Panel placed no ingredients in Category I, 10 ingredients in Category II, and 25 ingredients in Category III as antimicrobials. The Panel placed two ingredients in Category I, one ingredient in Category II, and no ingredients in Category III as astringents. The Panel placed three ingredients in Category I, one ingredient in Category II, and no ingredients in Category III as debriding agents. The Panel placed no ingredients in Category I, no ingredients in Category II, and two ingredients in Category III as decongestants. The Panel placed four ingredients in Category I, no ingredients in Category II, and no ingredients in Category III as demulcents. The Panel placed no ingredients in Category I, one ingredient in Category II, and three ingredients in Category III as expectorants. (The number of ingredient classifications does not equal the number of ingredients reviewed because some ingredients were reviewed for more than one labeled use.)

**Submission of Data and Information**

Pursuant to the notice published in the **Federal Register** of July 20, 1973 (38 FR 19444) requesting the submission of data and information on OTC oral health care drugs, the following firms made submissions relating to the indicated products that, the Panel has further determined, contain active ingredients or labeling which may be appropriately classified as oral health care drug products.

*A. Submissions By Firms*

**Firms and Marketed Products**

Ayerst Laboratories, New York, NY 10017; Larylgan throat spray
BASF-Wyandotte Corp., Wyandotte, MI 48192; Pluronic polyols
Beecham Products, Parsippany, NJ 07054; Dyclonine hydrocloride lozenges
Blair Laboratories, Inc., Norwalk, CT 06856; Isodine concentrate
Block Drug Co., Inc., Jersey City, NJ 07302; Proxigel
Calgon Consumer Products Co., Inc., Pittsburgh, PA 15236; Sucrets cold decongestant formula lozenges, Sucrets cough control formula lozenges, Sucrets sore throat lozenges
Church and Dwight Co., Inc., Syracuse, NY 13201; Arm and Hammer baking soda
Ciba-Geigy Corp., Summit, NJ 07901; Domiphen bromide
Colgate-Palmolive Co., Piscataway, NJ 08854; Benzethonium chloride mouthrinse
Cooper Laboratories, Inc., Cedar Knolls, NJ 07927; Amosan, oral-B antiseptic drops
Cox Drugs, Biltmore, NC 28803; Formula "U"
Denver Chemical Manufacturing Co., Stamford, CT 06904; Pain-A-Lay
Endo Laboratories, Inc., Garden City, NY 11530; Benzocol, Dyclocol, Lidocol
Glenbrook Laboratories (Division of Sterling Drug, Inc.), New York, NY 10016; Campho-Phenique
Hoyt Laboratories, Needham, MA 02194; Orabase with Benzocaine
Hynson, Westcott and Dunning, Inc., Baltimore, MD 21201; Thantis lozenges
International Pharmaceutical Corp., Warrington, PA 18976; Gly-Oxide liquid
Johnson and Johnson, New Brunswick, NJ 08903; Micrin plus, gargle and rinse
K. I. K. Co., Bethlehem, PA 18016; Cheramist
LaWall and Harrison Research Laboratories, Inc., Philadelphia, PA 19146; Troutman's cough syrup
Lorvic Corp., The, St. Louis, MO 63134; Odara solution
McKesson Laboratories, Fairfield, CT 06430; Isodettes anesthetic throat lozenges
Merrell-National Laboratories, Cincinnati, OH 45215; Cepacol anesthetic troches, Cepacol mouthwash/gargle, Cepacol throat lozenges
Monsanto Industrial Chemicals Co., St. Louis, MO 63166; Methyl salicylate
Norwich-Eaton Pharmaceuticals, Norwich, NY 13815; Chloraseptic aerosol spray, Chloraseptic lozenges, Chloraseptic mouthwash/gargle
Plough, Inc., Memphis, TN 38101; Aspergum
Procter and Gamble Co., The, Cincinnati, OH 45202; Scope mouthwash and gargle
Purdue Frederick Co., The, Norwalk, CT 06856; Betadine mouthwash/gargle
Reed and Carnrick Pharmaceuticals, Kenilworth, NJ 07033; Mouthwash and gargle
Rystan Co., Inc., White Plains, NY, 10605; Chloresium Dental ointment, Chloresium solution, Chloresium tablets
Schmid Laboratories, Inc., Little Falls, NJ 07424; Potassium chlorate, Ferric chloride, Balsam tolu, Glycerite of boroglycerin
Scott Laboratories, Inc., Corpus Christi, TX 78408; Scott's certified peroxide of hydrogen
Squibb Pharmaceutical Co., Princeton, NJ 08540; Spect-T decongestant lozenges, Spect-T cough suppressant lozenges, Spect-T anesthetic lozenges, Spect-T sore throat spray

Sterling Drug, Inc., New York, NY 10016; Campho-Phenique liquid, Campho-Phenique powder
Thayer, Henry, Co., Cambridge, MA 02138; Thayer slippery elm throat lozenges
Upjohn Co., The, Kalamazoo, MI 49001; Oral pentacresol
Vick Chemical Co., New York, NY 10017; Vicks medi-trating throat lozenges, Vicks oracin throat lozenges
Warner-Lambert Co., Morris Plains, NJ 07950; Listerine antiseptic, Listerine throat lozenges
Warren-Teed Pharmaceuticals, Inc., Columbus, OH 43215; Di-O-Chrome
Whitehall Laboratories, Inc., New York 10017; Anbesol

### *B. Ingredients Reviewed by the Panel*

#### 1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Acetanilid
Alcohol
Alum
Ammonium chloride
Anise oil
Antipyrine
Aromatics
Aspirin
Benzethonium chloride
Benzocaine
Benzoic acid
Benzyl alcohol
Borax
Boric acid
Boroglycerin
Calcium chloride
Calcium silicate
Camphor
Caramel
Carbamide peroxide
Carbolic acid
Cetyldimethylbenzylammonium chloride
Cetylpyridinium chloride
Chloroform
Chlorophyll "A" water-soluble derivatives
Cinnamon oil
Cresol
Dextromethorphan hydrobromide
Dextrose
Dibucaine hydrochloride
Domiphen bromide
Dyclonine hydrochloride
Elm bark
Essential oils
Eucalyptol
Eucalyptus oil
Ferric chloride
Gelatin
Gentian violet
Glycerin
Glycerol, anhydrous
Hexylresorcinol
Honey
Horehound
Hydrogen peroxide
Iodine
Isobornyl acetate
Lidocaine
Lidocaine hydrochloride
Menthol
Merodicein
Methylparaben
Methyl salicylate
Pectin
Peppermint oil
Phenol
Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride
Phosphate buffers
Plasticized hydrocarbon gel (polyethylene in mineral oil)
Potassium chlorate
Potassium chloride
Potassium iodide
Povidone-iodine
Povidone-iodine, concentrate
Propylene glycol
Propylparaben
Pyrilamine maleate
Sage oil
Saligenin
Secondary-amyltricresols
Sodium bicarbonate
Sodium bitartrate buffer
Sodium borate
Sodium caprylate
Sodium carboxymethylcellulose
Sodium chloride
Sodium dichromate
Sodium perborate
Sodium peroxyborate monohydrate
Sodium phenolate
Sodium saccharin
Sorbitol base
Spearmint oil
Sugar
Talcum power
Thymol
Tincture of myrrh
Tolu balsam
Urea peroxide
Vegetable stearate
Water
Wintergreen oil
Zinc chloride

#### 2. *Other ingredients reviewed by the Panel.*

Benzalkonium chloride
Dequalinium chloride
Dibucaine
Nitromersol
Oxyquinoline sulfate (8-hydroxyquinoline)
Tetracaine
Tetracaine hydrochloride
Thymol iodide

### *C. Classification of Ingredients.*

#### 1. *Active ingredients.*

**Anesthetics/Analgesics**

Antipyrine
Aspirin
Benzocaine
Benzyl alcohol
Camphor
Cresol
Dibucaine
Dibucaine hydrochloride
Dyclonine hydrochloride
Eucalyptol (eucalyptus oil)
Hexylresorcinol
Lidocaine
Lidocaine hydrochoride
Menthol
Methyl salicylate (wintergreen oil)
Phenol (carbolic acid)
Phenolate sodium (sodium phenolate)
Pyrilamine maleate
Salicyl alcohol (saligenin)
Tetracaine
Tetracaine hydrochloride
Thymol

**Antimicrobial Agents**

Benzalkonium chloride
Benzethonium chloride
Benzoic acid
Boric acid
Boroglycerin glycerite (boroglycerin)
Camphor
Carbamide peroxide in anhydrous glycerin (carbamide peroxide, urea peroxide)
Cetalkonium chloride (cetyldimethylbenzylammonium chloride)
Cetylpyridinium chloride
Chlorophyll (chlorophyll "A" water-soluble derivatives)
Cresol
Dequalinium chloride
Domiphen bromide
Ethyl alcohol (alcohol)
Eucalyptol (eucalyptus oil)
Ferric chloride
Gentian violet
Hydrogen peroxide
Iodine
Menthol
Meralein sodium (merodicein)
Methyl salicylate (wintergreen oil)
Nitromersol
Oxyquinoline sulfate (8-hydroxyquinoline)
Phenol (carbolic acid)
Phenolate sodium (sodium phenolate)
Potassium chlorate
Povidone-iodine (povidone-iodine, concentrate)
Secondary amyltricresols (secondary-amyltricresols)
Sodium caprylate
Sodium dichromate
Thymol
Thymol iodide
Tincture of myrrh
Tolu balsam

**Astringents**

Alum
Tincture of myrrh
Zinc chloride

**Debriding Agents**

Carbamide peroxide in anhydrous glycerin (carbamide peroxide, urea peroxide)
Hydrogen peroxide
Sodium bicarbonate
Sodium perborate (sodium peroxyborate monohydrate

**Decongestants**

Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride

**Demulcents**

Elm bark
Gelatin
Glycerin
Pectin

**Expectorants**

Ammonium chloride
Horehound
Potassium iodide
Tolu balsam

2. *Inactive ingredients.* The Panel has classified the following as inactive ingredients or pharmaceutical necessities. The list is not intended to be exhaustive.

Acetanilid
Anise oil
Aromatics
Calcium chloride
Calcium silicate
Caramel
Cinnamon oil
Dextrose
Essential oils
Glycerol, anhydrous
Honey
Isobornyl acetate
Methylparaben
Peppermint oil
Phosphate buffers
Plasticized hydrocarbon gel (polyethylene in mineral oil)
Potassium chloride
Propylene glycol
Propylparaben
Sage oil
Sodium bitartrate buffer
Sodium borate (borax)
Sodium carboxymethylcellulose
Sodium chloride
Sodium saccharin
Sorbitol base
Spearmint oil
Sugar
Talcum power
Vegetable stearate
Water

3. *Ingredient previously reviewed by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products in the* **Federal Register** *of September 9, 1976 (41 FR 38312).* Dextromethorphan hydrobromide.

4. *Ingredient removed from all drug products.* On June 29, 1976, a notice was published in the **Federal Register** (41 FR 26845) which prohibited the use of chloroform as an ingredient (active or inactive) in drug products. Studies conducted by the National Cancer Institute demonstrated that oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats. Section 310.513 (21 CFR 310.513) was established to remove chloroform from all drug products.

*D. Referenced OTC Volumes*

The "OTC Volumes" cited throughout this document include submissions made by interested persons in reponse to the call-for-data notice published in the **Federal Register** of July 20, 1973 (38 FR 19444). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after June 24, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

## II. General Statements and Recommendations

*A. Definitions*

The following are definitions of terms used in this document.

1. *Antimicrobial agent.* A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction and contributes to claimed effects of the product in which it is included.

2. *Antimicrobial preservative.* A compound or substance that kills organisms or prevents or inhibits their growth and reproduction and is included in a product formulation only at a concentration sufficient to prevent spoilage or prevent growth of inadvertently added microorganisms, but does not contribute to the claimed effects of the product to which it is added.

3. *Astrigent.* An agent that causes contraction of the tissues or arrest of secretions by coagulation of proteins on a cell surface.

4. *Bioavailability.* The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action.

5. *Decongestant.* An agent that reduces congestion or swelling. In OTC use for mucous membranes the term generally refers to adrenergic drugs that act by vasoconstriction.

6. *Debriding agent.* An agent which causes the removal of foreign material or devitalized or contaminated tissue from or adjacent to a traumatic or infected lesion to expose surrounding healthy tissue.

7. *Demulcent.* A bland, inert agent that soothes and relieves irritation of inflammed or abraded surfaces such as mucous membranes.

8. *Expectorant.* An agent that promotes the expectoration (spitting) of mucus or of respiratory tract secretions by decreasing the viscosity.

9. *Gargle.* A fluid, usually flavored or medicated or both, but not necessarily so, which is intended to be used to rinse or bathe the posterior part of the oral cavity, with the additional intent to expel mucus from the throat.

10. *Germicide.* An agent that destroys microorganisms. The term includes bactericide, fungicide, virucide, and amebicide.

11. *Hydrophilic.* A substance which has a marked affinity for water.

12. *In vitro study.* A laboratory study on the physical, chemical, or therapeutic properties of an agent. Such a study is not performed in living animals or people. An in vitro study may be done in laboratory equipment with material excised from the body.

13. *In vivo study.* A study performed in living animals or people.

14. *Iodophor.* There are at least three categories of iodophors: (1) Hydroalcoholic solutions of elemental iodine and iodides, (2) elemental iodine complexed with various surfactant compounds, and (3) elemental iodine complexed with various nonsurfactant compounds such as PVP-iodine complex (povidone-iodine).

15. *Lipophilic.* A substance with a pronounced affinity for fats (lipids).

16. *Mouth odor.* A general term for an odor emanating from the oral cavity. It may or may not be offensive. When such odor is perceived as unpleasant, obnoxious, offensive, or objectionable, a term such as "malador," "halitosis," or "bad breath" is used.

17. *Mouthwash.* A solution used for rinsing the mouth, not necessarily for medicinal purposes.

18. *Oleoresin.* A natural combination of a volatile oil and a resin, such as exudes from pines and other plants.

19. *Oral cavity.* The cavity of the mouth and associated structures, including the cheeks, palate, oral mucosa, glands whose ducts open into it, the teeth, and the tongue. For purposes of this Panel, the teeth and gums are excluded since they were considered by the Advisory Review Panel on OTC Dentifrices and Dental Care Drug Products.

20. *Oral health care.* The proper care of the mouth, including the temporary relief of symptoms of the mouth and throat, for example, occasional minor sore throat or mouth soreness.

21. *Organoleptic.* A property of a substance which makes an impression upon one or more of the organs of special sense (such as taste or smell), thereby affecting the flavor, odor, or appearance of a drug product.

22. *Pharynx (throat).* The musculomembranous sac between the mouth and nostrils and the esophagus. It is continuous below with the esophagus and above communicates with the mouth, nasal passages, and auditory (Eustachian) tubes. It is subdivided into the following parts:

(a) *Nasopharynx.* The part above the level of the soft palate.

(b) *Oropharynx.* The part that lies between the soft palate and the upper edge of the epiglottis.

(c) *Laryngopharynx.* This lies between the upper edge of the epiglottis and opens into the larynx and esophagus (sometimes called hypopharynx).

23. *Sialagogue.* An agent which promotes the flow of saliva.

24. *Topical analgesic.* A substance applied to an epithelial surface (e.g., skin or mucous membrane) that relieves pain without necessarily abolishing other sensations; or one that causes partial blockade of subcutaneous or submucosal terminal nerve endings so that a minimal stimulus evokes no painful response, but a greater stimulus does. In this document the term anesthetic has been adopted to conform with established ursage. Adoption of the term "anesthetic" does not preclude the use of the term "analgesic" when appropriate or preferable.

25. *Topical anesthetic.* A substance applied that completely blocks pain receptors resulting in a sensation of numbness and abolition of responses to painful stimuli.

*B. General Discussion*

1. *Introduction.* The Panel was convened and charged to evaluate ingredients in OTC preparations used for oral health care. These ingredients are intended to be used for the temporary relief of symptoms due to minor irritations, inflammations, and other lesions on the mucous membrances of the oral cavity (mouth) and pharynx (throat). Ingredients intended for the relef of symptoms airising from the teenth and gums were not evaluated by the Panel because ingredients for such use were reviewed by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products. The Oral Cavity Panel has reviewed these ingredients and evaluated them strictly from the standpoint of the symptomatic relief that they are intended to promote. The ingredients evaluated are applied directly to the mucous membranes of the mouth and throat and act locally. They are not intended to be curative, nor are they intended to be used by consumers in the self-diagnosis and treatment of afflications of the mouth and throat. Ingredients known or presumed to be absorbed and to act systemically were either deferred to other Panels for evaluation or classified as Category II. The Panel emphasizes that the ingredients evaluated by the Panel relieve symptoms that are self-limiting and that these ingredients are not for use as curative agents.

The Panel was charged to evaluate individual ingredients for safety and effectiveness for indications claimed in the labeling of OTC products in light of present-day knowledge and standards used in pharmacology, therapeutics, and toxicology. In making its evaluation, the Panel relied heavily upon factual data found in standard textbooks and scientific articles published by independent investigators in medical, dental, and other scientific journals. Some of these articles were incorporated by manufacturers into their submissions to the FDA to provide a scientific basis for claims made for the safety and effectivness of their ingredients. Data supplied by manufacturers in unpublished reports of studies performed by private laboratories under contract to the manufacturers or in manufacturers' laboratories were also used by the Panel in making judgments. The Panel also gave due consideration to data from marketing experience and widespread clincial usage. The Panel regards such data as corroborative when in agreement with basic data from controlled studies and scientific facts. The Panel placed little reliance upon such data, however, when insufficient pharmacologic, therapeutic, and toxicity studies were supplied. The Panel felt it was under no obligation to make a judgment on the safety and effectiveness of ingredients relying solely on marketing data supplied by the manufacturers in their submissions.

The Panel has considered the ingredients in the submissions and has grouped them according to their pharmacologic activity and modes of action. It has deferred to other Panels for consideration, or classified as Category II, those ingredients believed to exert their claimed effects systemically after absorption from the mucous membrances of the oral cavity or those ingredients that have no effect on the mucous membrances.

In its review of ingredients of oral health care products, the Panel has identified two groups having a general similarity based on indications for recommended use. The first group, consisting principally of mouthwashes, rinses, or sprays, is offered for cleansing of the mouth, elimination of mouth odors, and other hygienic or cosmetic purposes. In most cases products in this group are recommended for use on a continuing basis in situations in which no symptoms or evidence of disease are present. Many are recommended for use on a day-to-day basis with no specified limits on time or quantities of usage. Some are recommended for prophylaxis for oral cavity diseases.

The products in the second group are offered for short-term therapy to relieve symptoms of sore throat and sore mouth. Definite evidence of a pathologic process exists, and a limit has been placed on the time the product is recommended for use. In some cases, overlapping exists and the indications of the first group also encompass some of the indications for products in the second group. The Panel has evaluated the ingredients in each of the products in these groups on the basis of therapeutic effectiveness in relieving symptoms of pathologic processes given rise to sore mouth or sore throat or both. Claims made for ingredients in oral health care products that do not meet these criteria, i.e., relief of symptoms, are considered to be Category II claims.

Some products list active ingredients for which no claim for indications for use are made in the labeling. Products containing such ingredients are considered to be misbranded.

The Panel has identified the major pharmacologic groups as listed below from the claims made for the active ingredients in the labeling of OTC products. The active ingredients are discussed in statements, elsewhere in this document, according to this pharmacologic classification. Certain drugs have more than one action and have more than one therapeutic claim made for such actions. Therefore, such ingredients appear under two or more different pharmacolgic classes in the ingredient discussions below. Phenol, for example, is claimed to exert both a topical anesthetic effect and an antimicrobial effect. The Panel has considered the chemistry, pharmacology, toxicology, safety, and effectiveness of phenol in the discussions of this ingredient. Its safety and effectiveness are discussed first as an anesthetic in the section on anesthetics/analgesics. (See part III. paragraph b.l.g. below—Phenol.) The effectiveness of phenol as an antimicrobial agent is then described in the section on antimicrobial agents. (See part IV. paragraph B.3.r. below—Phenol.)

The Panel has identified the following pharmacologic groups of ingredients and described each one, their modes of action, and their effects, elsewhere in this document:

a. Anesthetics/Analgesics.
b. Antimicrobial agents.
c. Astringents.
d. Debriding agents.
e. Decongestants.
f. Demulcents.
g. Expectrorants.

Anesthetics may also be recognized as analygesics. It is well known and accepted that anesthetics, in low concentrations, may and will usually act as analgesics. However, not all

analgesics exert an anesthetic effect at higher doses. The Panel has adopted the term "anesthetic/analgesic" in this document for the purpose of grouping these ingredients for ease of review. Adoption of this term does not preclude the use of the terms "anesthetic" or "analgesic" in labeling, as appropriate, and the Panel leaves the choice of selecting either of these terms to the manufacturer. The Panel, however, concludes that it is not acceptable to use the term "anesthetic" in the labeling of a product which contains an analgesic, i.e. aspirin, as its only active ingredient.

An ingredient having more than one pharmacologic action, as for example phenol, may be classified in one category (Category I) as an anesthetic and in another category (Category III) as an antimicrobial agent. Other ingredients in more than one pharmacologic group for use on the mucous membranes of the mouth and throat have similarly been evaluated by the Panel for their safety and effectiveness.

The mouth and throat are continuous with the lower respiratory and gastrointestinal tract. There are many ingredients that may act on the mucous membranes of these structures. However, these ingredients are considered primarily from the standpoint of the effect that they exert on the mucous membranes of the mouth and throat.

In some cases, the action of certain drugs may be selective and exert a greater effect in some tissues than in others. In other cases, the responses of drugs and their differences are merely quantitiative and relative, and depend upon the number of cells or receptors on the cells being affected. Various degrees of predilection for certain cells may occur with changes in conditions, or dosage, or pH, etc. The mechanism and selective action of the drug may depend upon differences of penetration or upon chemical affinity of the drug for the cells or the changes in the sensitivities to the action of the drug. The drug may also act on the cell without actually penetrating into it, as for example, by exciting or depressing the nerve supplying the cell. A drug may act directly on the cell surface and alter its function by withdrawing water from the cytoplasm. As a general rule, the drug must pass into the cell or cell membrane before it can exert any action, and, in order for absorption to occur, the drug must be soluble in the constituents of the cell membrane. The solubility of a drug in the cell membrane and cytoplasm is not necessarily the same as it is in water. It may vary for each kind of cell, and consequently the penetration of drugs into the different cells may vary (Refs. 1, 2, and 3).

In some cases, a concentration of a sustance that accumulates in a cell may be greater than that present in the external environment. This concept holds true expecially if the substance undergoes selective concentration. This may be due to the fact that the ingredient binds with proteins and cell constitutents and attains a concentration that is pharmaceutically active. Some of the aforementioned principles apply to absorption from the mucous membranes of the mouth and throat and are described in more detail below.

**References**

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2. *Oral health care.* The Panel has adopted the term "oral health care" in referring to the use of products intended for the relief of symptoms due to pathologic states in the mouth and throat and refers to these products as oral health care products. The Panel is aware of the widespread use of the term "oral hygiene" and the fact that it is in some cases used to support therapeutic claims for pathologic states in the mouth in the labeling of some oral cavity products. Consumers associate the term with cleansing agents and other cosmetic products for use in the mouth on a daily basis or more often. The Panel feels that the term "oral hygiene" should be reserved exclusively for use in the labeling of cosmetic products used for cleaning and similar purposes to maintain a healthy state of the mouth and not for identifying a product as one having therapeutic claims. The Panel, therefore, considers labeling such as "for oral hygiene" a Category II claim if a product having such labeling is intended to be used for therapeutic purposes.

The mouth and nose are the portal of entry of a variety of microorganisms (Ref. 1). These may remain in the mouth, nasopharynx, and throat, or they may remain in the gastrointestinal tract or respiratory system. Normally they do not cause disease. The oral cavity is endowed with physiologic mechanisms for maintianing a healthy state of the structures contained therein. In essence, no medications are needed to achieve this end. The secretions of the salivary, mucous, and serous glands lubricate and maintain a healthy state of the mucous membrances and other structures in the mouth. The indigenous flora of the oral cavity consits of nonpathogenic microorganisms which seldom produce disease. They help maintain a balance of the microbial population and probably play an important role in maintianing a healthy state of the oral cavity.

Normally, approximately 0.25 to 1.0 milliliter (mL) of saliva is excreted per minute or about 1,500 mL per 24 hours. This, together with the secretions of the mucous glands, acts as a diluent, has a cleansing action, and moistens the mucous membrances. It cleans the mouth and teeth and may inhibit bacterial growth. The flow of saliva can be modified by various normal stimuli (Refs. 2, 3, and 4).

In addition to the above-mentioned protective mechanism, immunologic defense mechanisms, particularly those involving the action of immunoglobulin A (IgA), are also present. These interfere with adherence of microogranisms to mucosal surfaces by causing them to aggregate, rendering them susceptible to phagocytosis (Refs. 1, 5, and 6).

In fever and during certain illnesses, the flow of saliva and secretion of mucus may be decreased. Orgnic material may accumulate and decompose, and bacterial growth is no longer inhibited. A foul odor may develop, and ulcerations and inflammation of the mucous membrances may result (Ref. 2). Sore mouth, discomfort, or pain may also develop, making treatment desirable. Since a pathologic state exists in such situations, claims may be made for the use of OTC oral health care products to relieve these symptoms. However, the labeling should clearly indicate that if the symptoms persist, professional advice should be sought. It is the consensus of the Panel that claims implying that an OTC product can be used for oral health care and can prevent the development of such a pathologic state in a person who is not in good health are not acceptable. Claims that state or imply that the prophylactic use of an OTC oral health care product maintains a healthy state are misleading to a consumer.

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3. *The anatomy and physiology of the oral cavity.* The oral cavity extends from the lips to the anterior pillars of the fauces and is lined by the oral mucous membrane. The mucous membrane is composed of connective tissue covered by stratified squamous epithelium. Modifications of this basic pattern occur in different areas of the mouth and are related to differing functions. The hard palate, gingiva, and the tips of the papillae on the dorsum of the tongue are the only areas where keratinization normally occurs in the oral cavity of human beings.

a. *The oral mucous membrane.* The oral cavity is concerned with proprioception, taste, and mastication (chewing) of food. During the process of mastication, the food is mixed with saliva and the enzymes in the saliva initiate digestion. Stern (Ref. 1) divides the oral mucosa into three major types: (1) Masticatory mucosa (gingiva, hard palate); (2) lining or reflecting mucosa (lip, cheek, vestibular fornix, alveolar mucosa, floor of mouth, and soft palate); and (3) specialized mucosa (dorsum of the tongue and taste buds).

The masticatory mucosa is bound to bone and does not stretch. The lining mucosa covers the musculature and is distensible. It covers all the surfaces of the mouth except the dorsum of the tongue and the masticatory mucosa. The specialized (sensory) mucosa bears the taste buds, which have a sensory function.

The oral mucous membrane is composed of two layers, epithelium and connective tissue (lamina propria). The dermal papillae contain blood vessels and nerves and interdigitate with the epithelial ridges. At the junction of the two tissues are the basal lamina and the basement membrane. The basal lamina is not ordinarily discernible with the light microscope, but is evident at the electron misroscopic level and is epithelial in origin. The basement membrane is evident at the light microscopic level. It is a relatively cell-free zone that is 1 to 4 microns thick and found within the connective tissue, subjacent to the basal cells. This zone stains positively with the periodic acid-Schiff method, indicating that it contains neutral mucopolysaccharides (glycosaminoglycans). It also contains fine argyophilic silver staining reticular fibers, as well as special anchoring fibrils.

The lamina propria may be attached to the periosteum of the alveolar bone, or it may overlay the submucosa, which varies in thickness in different regions of the oral cavity, such as the floor of the mouth and the soft palate.

The submucosa attaches the mucous membrane to the underlying structures. Within this layer are glands, blood vessels, nerves, and adipose tissue. The sensory nerves to the mucous membrane tend to be more concentrated at the anterior part of the mouth. The nerve fibers are myelinated in the submucosa, but lose their myelin sheaths before splitting into their end arborizations. Sensory nerve endings of various types are found in the papillae. Some of the fibers enter the epithelium, where they terminate between the epithelial cells as free nerve endings. The blood vessels are accompanied by nonmyelinated visceral nerve fibers that supply their smooth muscle. In those areas of the mouth where the submucosa is lose, the mucous membrane is movable over the deeper layer. On the other hand, where the submucosa is dense the mucous membrane does not move over the deeper structures.

The epithelium of the oral mucosa is stratified squamous. It may be keratinized, parakeratinized, or nonkeratinized depending on location. In the oral cavity of humans, only the gingiva and the hard palate are normally keratinized, although in many individuals the gingival epithelium is parakeratinized. The cheek, faucial, and sublingual tissues are normally nonkeratinized.

The four cell layers which are found in keratinizing oral epithelium are the basal, spinous, granular, and cornified layers. The basal cell which ultimnately forms keratin at the surface is called the keratinocyte.

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b. *The physiology of pain.* Pain is difficult to define. There is little point in attempting to formulate a definition of a subjective sensation that is clearly known to each individual by experience and the nature of which is described by illustration. Pain is the most common symptom for which people seek relief. It is an experience that embodies both the capacity to be discriminative and the ability to interpret the nature of a stimulus by reference to present and past experiences (Ref. 1).

Obviously, it is best to determine the etiology of a pain and treat the causative factor, be it a disease process, the result of trauma, or a functional disturbance. Nonetheless, self-limited, mild to moderate pain in the mouth and throat may be treated symptomatically by self-medication.

Sensory receptors are present in the mucous membranes, the submucosal tissues, and the muscular and other structures of the oral cavity for the perception of pain, cold, warmth, touch, pressure, proprioception, and taste (Refs. 2 and 3). A discussion of receptors for pain, cold, warmth, touch, and pressure follows because they are stimulated by certain ingredients used in oral health care products such as camphor, menthol, etc. Furthermore, if subjected to greater-than-ordinary stimulation they may be sensed as pain. Receptors for taste are located in the tongue and are discussed below along with the receptors for smell, which are located in the nose. The receptors for taste and smell act in consort, since what a person interprets as taste may actually be due to smell. Since many drug preparations used in the oral cavity contain distasteful ingredients and flavors, odoriferous ingredients are added to assure patient acceptance. Therefore, the sensations of taste and smell assume importance in OTC oral health care products and are discussed below. (See part II. paragraph B.3.c. below—The physiology of taste. See also part II. paragraph B.3.d. below—The physiology of smell.)

Topical anesthetics act at the site of application of a drug after they penetrate the mucous membranes and come into contact with these sensory receptors. These receptors are connected to terminal fibers of networks of nerves that are present in the various layers of the epithelial membrane and other tissues.

Each type of receptor ordinarily perceives its own type of sensation. They can also respond to thermal, mechanical, chemical, or painful stimuli and induce the sensation of pain. Stimuli of greater intensity than normally required to activate them may produce the sensation of pain. Sensory receptors are classified as follows: (1) *Receptors for pain.* These consist of "bare" nerve endings that receive the stimuli incited by pain directly and transmit them along larger nerve trunks to the central receptors in the brain. Itching is not ordinarily perceived in the oral cavity; yet it has been perceived on rare occasions, particularly in areas covered by stratified squamous epithelium or at the mucocutaneous junctions. The sensation of itch is carried along the same receptors as that of pain. The principal difference is that the intensity of the stimulus or the frequency of impulses for inducing itch are less than the impulses for inducing pain (Refs. 3 and 4). The nerve fibers carrying the sensation of pain and itch are mostly of the small unmyelinated C type sensory nerve fibers (Ref. 1). Some delta A myelinated fibers may also play a role. Pain fibers are not uniformly distributed over the mucous surfaces. They are more concentrated on the tongue, in the pharynx, along the lips, and less so in areas such as the palate and floor of the mouth. The activity of these receptors is obtunded partially or completely by topical analgesics and anesthetics. The modes of action of analgesics and anesthetics are described below. (See part III. paragraph A.1. below—Modes of action.) The pain receptors appear to be affected more easily and readily than the receptors for other sensations listed above probably because they are small and unmyelinated nerve fibers and are thereby easily penetrated by drugs (Ref. 3).

(2) *Receptors for cold.* The end bulbs of Krause are oval sense organs that perceive the sensation of cold. These nerve endings may be blocked simultaneously with the pain receptors by topical anesthetics. Whether or not they are blocked depends upon the concentration of anesthetic that reaches them and the degree of penetration. They may be stimulated by some ingredients, such as menthol or camphor, and produce a sensation of coolness that masks the sensation of pain. Some counterirritants may act by stimulating these receptors. Counterirritants and rubefacients, however, have no place as therapeutic agents in OTC oral health care products.

(3) *Receptors for warmth.* The end organs of Ruffini are cylindrical end organs in the mucous membranes that perceive the sensation of warmth. They may also be partially or completely blocked simultaneously by anesthetic ingredients, depending upon the concentration and the duration of contact of the ingredient. These receptors are stimulated by some ingredients, such as camphor and alcohol, by some flavorants, and by some rubefacients, such as methyl salicylate, which are all present in OTC oral health care products.

(4) *Receptors for pressure.* Pacinian Corpuscles are cylindrical end organs in the skin that perceive the sensation of deep pressure. Anesthetics in concentrations exceeding those needed to block pain receptors may be needed to block these receptors.

(5) *Receptors for touch.* Meissner's corpuscles are end organs in the mucous membranes that perceive the sensation of touch and respond to tactile stimuli. They may also be partially or completely blocked by anesthetics (Refs. 2 and 3). They may be stimulated by the presence of exudates, mucous, and other secretions that collect on mucous membranes.

Pain on epithelial surfaces is well-defined and easily localized. Pain arising in structures beneath the mucous membranes may be poorly localized and is usually dull in character. It may, however, be sharp in some cases and spread or radiate in a distinct pattern. Pain is frequently "referred," i.e., felt at locations remote from its source (Refs. 3 and 4). It is not uncommon to experience deep-seated pain in structures in the oral cavity or the pharynx, Pain arising from a localized aphthous ulcer beneath the tongue, for example, may radiate along the entire lower jaw to the tongue, into the nose or even the head. Pain in the pharynx may radiate to the ear via the anterior or posterior pillars to the Eustachian tube. The oral cavity is richly supplied with sensory receptors from filaments of the fifth cranial nerve. Most structures in the mouth are extremely sensitive to painful as well as other stimuli. In addition, the ninth cranial (glossopharyngeal) nerve as well as filaments of the tenth cranial (vagus) nerve also provide a sensory supply to the posterior portion of the tongue, and oro-and hypopharynx, The ability to identify and localize pain is not inborn; it is learned from past experience.

Pain originating from bones, joints, and tendons may induce muscle spasm and cause pain in the affected muscles. Induced spasm or chronic muscle injury, with pain, is a part of an involuntry defensive mechanism whereby the patient attempts reflexively to immobilize a painful joint (Ref. 5). This is not uncommon in the oral cavity when spasm of the muscles of mastication attempt to immobilize the temporomandibular joint. The muscles of the pharyngeal wall may also go into spasm when swallowing occurs in cases of sore throat.

Relief of pain involves two components: raising the pain threshold and altering the psychologic response to pain. The pain threshold varies little from one individual to the next, but the psychological response to pain varies greatly among individuals and in the same individual under different circumstances and in different settings. What may be referred to as a slight pain by one individual may be interpreted as a severe pain by another. Time, place, environmental and social factors, cultural background and family response patterns, emotional status, age, and past experiences may all influence an individual's response to pain and interpretation of the "meaning" of the stimulus. Anxiety is an important factor in the interpretation of pain. The number of individuals who experience pain in which there is no anxiety component is few, indeed (Refs. 1, 3, and 4).

The placebo effect is an important factor to be considered in the evaluation of pain, not only in OTC self-medication, but in all aspects of the healing arts. The psychosomatic contribution of the placebo effect in the evaluation of pain and drugs that relieve pain is a mandatory consideration in any well-designed and meaningful study. The response of an individual's pain perception to a placebo effect is independent of the cause of the pain or of the mechanism inducing the pain. It is more likely that it is discernible if pain is intense. The placebo effect is not peculiar to "neurotic" individuals, and it is not predictable (Refs. 1 and 6).

The intensity of a pain is not necessarily dependent on the severity of the lesion or the pathologic process causing it. A small aphthous ulcer beneath the tongue at the frenulum may cause marked discomfort and cause the pain to radiate into the tongue and lower jaw. On the other hand, a large circumscribed lesion on the hard palate may cause little or no discomfort. Many mouth and pharyngeal (throat) lesions cause little or no discomfort while the patient is quiet, does not talk or attempt to chew or swallow. Any of these activities may incite the pain. Discomfort may result when acidic liquids are ingested and come into contact with the lesions. On the other hand, such lesions of the mouth and throat are little affected or stimulated by

bland substances. Discomfort may also be felt when lesions are covered by exudates. Such discomfort may be relieved by removal of the exudates by using rinses, debriding agents, and in some cases astringents, or by the application of demulcents. The pain ususally recurrs when the exudate reappears.

The Panel concludes that OTC anesthetic/analgesic ingredients are useful for the treatment of the symptoms of occasional minor throat and mouth pain. A pain is usually described as either mild to moderate or severe. Moderate pain may be self-limited and require no special treatment or prior diagnosis by a physician. It is usually relieved by OTC drugs. In some cases, mild pain is referred to as a "minor irritation." Diagnosis and treatment by a physician may not be required for occasional minor irritations and minor pains. Anesthetics, therefore, are often desirable to reduce their intensity and provide relief and comfort. Individuals who must maintain normal daily activities often find these agents useful in providing comfort. The Panel emphasizes that none of the ingredients used in the oral cavity to relieve pain are curative.

The Panel concludes that the most appropriate indication for the relief of pain by OTC anesthetic/analgesic agents should state "for the temporary relief of occasional minor irritation, pain, sore throat, and sore mouth." The Panel recommends the use of the term "occasional" because recurrent or chronic pain, even though of minor intensity, may require diagnosis by a physician to determine the cause.

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c. *The physiology of taste.* Smell and taste are interrelated chemical senses. Their importance in patient acceptance of a product used in the oral cavity has been mentioned above. The receptors for taste are chemoreceptors which respond to chemical stimuli. A substance must first be dissolved to arouse a sensation of taste. It may be taken either in solution or dissolved in the saliva or mixed with moistened food or other ingredients. A solid that is placed in a perfectly dry mouth generally cannot be tasted (Refs. 1 through 4).

The anterior two-thirds of the upper surface (dorsum) of the tongue has numerous minute projections of the mucous membrane called papillae. The papillae at the edges, the tip, and the most anterior portion of the dorsum of the tongue are small, conical, cylindrical, or mushroom-shaped structures. They impart a velvety character to this part of the mucosa of the tongue. They are referred to as being filiform (threadlike) or fungiform (mushroomlike) in character, depending on their shape. The most posterior part of the tongue surface is rougher than the anterior due to the presence of papillae that are considerably larger than papillae on the anterior part of the tongue surface. These are peculiar in construction since each is surrounded by a groove or trench. The whole structure has been described as resembling a squat tower surrounded by a moat. They are, therefore, called "vallate papillae", after the Latin word "vallatus" meaning walled (Refs. 1 through 4).

Imbedded in the covering of both large or small types of papillae are groups of slender cells with hairlike processes that are packed lengthwise in bundles. The cells are the receptors of taste. The bundles are called tastebuds. Each cell receives a filament from one of the nerves of taste. The tastebuds open upon the surface of the papillae through a small pore. The ends of the cell converge toward this point where their processes become massed together. Substances in solution enter the pores and act as chemical stimuli. A few scattered tastebuds are present on the extreme posterior (pharyngeal) portion of the tongue and even in the mucosa of the epiglottis.

Four fundamental sensations of taste have been delineated: Sweet, bitter, sour, and salty. Two others are sometimes mentioned, alkaline and metallic. The various other types of tastes that are described are due to a blending of some or all of the fundamental sensations or to a combination of the latter with sensations caused by stimulation of ordinary sensory receptors of pain in the mouth that have been described above. (See part II. paragraph B.3.b. above—The physiology of pain.) Ginger, for example, is not recognized by its actual taste, that is, by stimulation of tastebuds, but by the burning sensation that results from excitation of the other sensory receptors in the mouth, such as those for warmth. Oils are unpleasant to taste, especially because of their consistency which causes a peculiar feeling due to stimulation of the receptors for touch. Acetic and other acids have a sour taste, but also give rise to a burning sensation since they act on other sensory receptors. This is confused in interpretation in the mind with the sense of taste and blended with it (Refs. 1 through 4).

Many of the finer flavors interpreted as tastes are in reality sensations of smell. Smell enters largely into the many sensations attributed to taste. For this reason, when the nose is held or the nasal mucous membrane is inflamed and the nasal passages are occluded, as by an ordinary cold, the sense of taste is blunted.

On the other hand, certain substances which are thought to be detected by smell are actually recognized by the sense of taste. Chloroform is an example of such a substance. The sweetish smell of chloroform is sensed when its vapor dissolves in the saliva reaching the tastebuds. In certain situations in which the first nerve, the olfactory nerve, which carries the sensation of smell, is injured by disease, trauma, or is paralyzed, the sensations of taste are obtunded or absent and perception of different tastes is impaired (Refs. 1 through 4).

The four fundamental taste sensations are not aroused with equal intensity over all parts of the surface of the tongue. Each type of taste sensation is served by its own type of tastebud. Taste receptors sensitive to sweetness and to saltiness are most numerous at the tip and fore part of the tongue. Those responding to sourness are found along the edges of the tongue. The tastebuds sensing bitter tastes are scattered over the back of the tongue and epiglottis. Some substances, such as sodium salicylate, have a bitter-sweet taste. When sodium salicylate is first taken into the mouth it comes in contact with the fore part of the tongue and tastes sweet, then the bitter element comes into play when the substance passes the posterior part of the tongue. Little or no sensation of taste can be aroused from the central portion of the tongue surface (Refs. 1 through 4).

The sense of taste is much less sensitive than the sense of smell. Sweetness, for example, is detected in a dilution of 1 part in 200; saltiness in dilution of 1 part in 400; sourness due to acids in a dilution of 1 part in 130,000; and bitterness, such as would be induced by quinine, by 1 part in 2,000,000 (Refs. 1 and 4).

Several nerves carry taste impulses from tastebuds. Those that subserve the tongue are the chorda tympani branch of the facial nerve and the glossopharyngeal nerve. The chorda tympani nerve supplies tastebuds over the anterior two-thirds of the tongue; the glossopharynegeal nerve supplies tastebuds over the posterior third. The fibers of the chorda tympani nerve are conveyed to the tongue in a trunk of the lingual nerve which is a branch of the mandibular division of the fifth nerve. The vagus nerve carries impulses from the extreme lower posterior portion of the tongue in the hypopharynx and from the surface of the epiglottis. The center for taste lies in the lower end of the somesthetic area of the cerebral cortex.

d. *The physiology of smell.* Smell is very closely allied to taste and has been described as "taste from a distance." In many animals, the sense of smell is incredibly acute, and a large proportion of the brain is concerned with this sense. In some species, the sense of smell is of paramount importance because smell is relied upon to warn of the approach of enemies, to guide an animal in the quest of food, and to sense direction. Even in humans, in whom the sense of smell is comparatively rudimentary, certain substances, for example, some mercaptans, can be detected in a dilution of one part in 30,000,000,000 or more parts of air (Refs. 2 and 3).

An odorous material continually emits particles of molecular size which are carried in the air to the olfactory receptors. Substances which pass readily into a vapor state or exist in a gaseous state, such as turpentine, gasoline, chlorine, and some essential oils, generally have strong ordors. Nonvolatile materials, on the other hand, such as heavy metals, are ordorless. In order to be smelled, a substance must reach the nose in a gaseous form (Refs. 2 and 3).

The mucous membrane of each lateral wall (or side wall) of the nasal cavity covers three ridges which arise from the lateral bony wall of the nasal cacity (superior, middle, and inferior turbinate or conchae). The interior of the nose is thus divided incompletely on each side into four compartments or regions, each region placed above the other. The lower three of these regions serve as air passages. They communicate with the outside via the nostrils at the front and with the pharynz at the rear. The uppermost compartment consists of a narrow cleft lying immediately beneath the anterior portion of the floor of the skull. The receptors for smell (olfactory receptors) are imbedded in a small patch of mucous membrane situated on each wall of this narrow space.This narrow space is a blind pocket from which the main air currents are excluded. Air containing the odorous particles must, therefore, be carried to the olfactory mucous membrane if an odor is to be perceived. This is done either by diffusion or by convection currents that result when the cooler inspired air meets the warmer air within the nose. When, for example, one wishes to smell a particular scent, an individual makes a quick, short sniff. The sharp inhaling of the cool outside air creates ascending convection currents which are conveyed to the inside of the blind pocket, which is the sensitive area and contains the receptors. The material does not act directly on the olfactory receptors, but must first be dissolved in a layer of fluid covering the mucous membrane. The similarity between the sense of taste and the sense of smell in this regard is of interest (Refs. 2 and 3).

There is an infinite variety of odors, and it is difficult to satisfactorily classify the different types of odors. An attempt has been made to group them under eight headings: (1) Ethereal, (2) aromatic (resinous), (3) fragrant (balsamic), (4) ambrosial, (5) garlic, (6) burning, (7) goat, and (8) foul. The blending of these various types gives rise to the different degrees of a particular odor that may be sensed. The olfactory epithelium is composed of spindle-shaped nerve cells distributed evenly among elongated cells which are purely supporting in function. Each dendrite, after emerging from between the supporting cells, divides into a tuft of some six or eight straight filaments which project a short distance beyond the epithelial surface. These pass through the perforations in the floor of the skull and enter the olfactory bulb, a primary olfactory center. Olfactory receptors adapt quite rapidly, and they soon no longer respond to some particular stimulus. It is well known that an order, though strong when first perceived, becomes imperceptible after a short period of time. This phenomenon of adaptation also observed among other types of receptors is not due to fatigue. The receptors still remain active because when some particular odor is no longer perceived another odor is readily perceived when the subject is exposed to it. In some individuals there is an inability to smell certain odors at all, even though there is no impairment of the olfactory sense. For example, hydrocyanic gas, which is a poison used for the extermination of vermin, has an odor of bitter almonds which is strongly perceived by some individuals and quite odorless to a small segment of the population (Refs. 2 and 3).

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e. *Absorption through mucous membranes.* Oral-health care products are applied topically to the mucous membranes of the mouth, or throat, or both to exert their therapeutic effect. They are usually applied in the form of rinses, gargles, sprays, swabs, drops, lozenges, or powders (Ref. 1) Powders ordinarily are used on the teeth; occasionally, they are used on the mucus membranes. Ointments are seldom used in the mouth and throat. When they are used, they are applied with the finger or with an applicator. With the exception of lozenges and powders, the duration of contact of most preparations, particularly those formulated in aqueous, nonviscous media, is relatively brief, unless liquid preparations are formulated in solvents that adhere to the mucous membranes. Liquid preparations mix with the saliva and are diluted and swallowed. Some drugs combine with cell proteins and exert a therapeutic effect as long as the combination persists. Lozenges permit a more prolonged contact than rinses, sprays, or swabs and are, as a rule, more effective (Ref. 1).

Many drugs are absorbed readily from the mucous membranes of the mouth and throat and promptly pass into the systemic circulation (Refs. 1, 2, and 3). Although drugs used in the oral cavity are not intended to be swallowed, invariably all or a portion of a dose passes into the stomach or intestinal tract where it may undergo complete

absorption. Lozenges and powders ultimately are swallowed, and most of their components are absorbed either in the stomach or in the intestinal tract (Refs. 3, 4, and 5).

There may be considerable absorption of oral health care preparations from the mucous membranes of the mouth even though the contact is brief. The entire gastrointestinal tract, commencing at the oral cavity including the lips and ending in the rectum, is lined by a sheath of closely packed epithelial cells that form a continuous hollow tube from the mouth to the rectum. When a substance is absorbed it must first enter epithelial cells and be transferred across them to reach the fluid in the lamina propria beneath the cells and finally pass into the blood and lymph and into the capillaries. A substance may also pass into the lymph and then into the blood. The cell membrane is essentialy a double layer of lipid molecules between the which is stretched a layer of proteins and polypeptides. The lipid materials are oriented both inward from the interior of the cell surface and outward from the exterior of the cell membrane. The cell membrane is a continuous phase. It is perforated by minute pores through which hydrophilic molecules, including water itself, may pass as well as other small molecules such as urea, glycerol, and small ions such as chloride and potassium. Certain drugs readily pass through the mucous membranes; others do so with difficulty. Nonpolar substances can pass with ease, usually by simple diffusion. This selectivity is apparent rather than actual and is due to physical, chemical, and biologic factors involving the drug, the cell membrane, or both. Passage of a drug through membranes, often referred to as transport, is accompanied by processes which are either active or passive. Passive transport, such as simple diffusion, requires no expenditure of energy. On the other hand, energy is necessary for active transport since the substances are moved against a chemical or electrical gardient. For example, during the process of restitution of the nerve membrane to its normal resting (polarized) state after passage of a nerve impulse along a nerve fiber, the sodium ions must be forced out of the interior of an axon from an area of low concentration to the exterior where the concentration is higher. Energy is required to accomplish this movement of sodium ions from an area of low density to one of higher density. The chief mechanisms of drug transfer across the membranes are described below (Refs. 3, 4, and 5).

Diffusion through the lipid phase of the cell membrane varies with each drug. Nonpolar lipophobic, hydrophilic substances dissolve in the cell membrane and cross by diffusion. Nonlipid-soluble substances that are highly ionized do not readily traverse the lipid membranes of cells. Ions cannot penetrate cell membranes since they are not lipid soluble. Lipid-soluble polar substances readily penetrate the cell membrane by diffusion. The ease of passage depends upon the lipid-water partition coeffient of a drug. The partition of a substance between a lipid and an equal volume of water is important. The greater the amount of a substance that passes from an aqueous phase of a solution when shaken with an oily substance, the greater the partition coefficient and the greater its ease of penetration through cell membranes. Penetration of a polar substance is favored by a high lipid-water partition coefficient. Certain substances are polar in an acid medium and nonpolar in an alkaline medium or vice versa. In the presence of weak acids and bases, penetration is favored by the presence of a high proportion of lipid-soluble, nonionized polar form of a drug (Refs. 3, 4, and 5).

Intravenous injection of a drug that is poorly ionized is followed by a rapid accumulation of a drug in the capillary-rich organs, such as the brain, heart, liver, lungs, etc., since penetration occurs readily through the membranes. The reverse is true in the case of highly ionized drugs. For instance, quaternary ammonium compounds, which as a rule are highly ionized, will not penetrate the blood-brain barrier due to their poor lipophilic qualities. If the pH on the two sides of a cell membrane is different, the distribution of a weak electrolyte on each side of the membrane will also be different. Only the un-ionized form is permeable and will penetrate until the concentration on each side of the membrane is the same and an equilibrium is attained. The amount of ionized form present will depend on the pH of the medium in which it is dispersed. This is the case if the ionized form and the total concentration is less on the acidic lumen side of the gastrointestinal tract than in the neutral bloodstream. A weak acid present in the lumen of the bowel is rapidly absorbed and passes into the blood, whereas a weak base present in the bloodstream rapidly leaves the bloodstream and is excreted into the lumen of the bowel. It has been shown that a weak acid, such as aspirin, which is poorly ionized in the stomach, is rapidly absorbed from the stomach. On the other hand, ephedrine, which is a weak base and readily forms a salt with the hydrocholoric acid of the stomach and is highly ionized, is not absorbed (Refs. 3, 4, and 5).

A factor which also influences the distribution of drugs across membranes is their degree of protein binding. For example, aspirin is more concentrated in blood plasma than in tissue fluids because of the greater protein content of the plasma. One of the reasons why few drugs distribute evenly between the extracellular and intracellular fluid is that there are differences in protein content in the two media, and the protein-bound fraction is unable to traverse the cell membrane. There are also differences in the nature of proteins in the two media and in the affinity of a drug for the different types of protein which also account for the differences in concentration (Refs. 3, 4, and 5).

In summary then, the following factors are involved in the transport of drugs across membranes. (1) *The filtration through pores.* Hydrophilic, lipid-insoluble substances cross membranes through water-filled pores where there is a hydrostatic or osmotic pressure difference across the membrane. Water flows in bulk through the membrane pores carrying with it small molecules whose dimensions permit passage through the pores. The evidence that supports this is obtained by meauring diffusion rates. The passage of most hydrophilic substances depends upon their molecular size or molecular radius. Pores in the membrane may allow the penetration of molecules of small size, such as those of urea, into cells. Larger molescules not permeable through pores may pass across the capillary wall into the bloodstream. For example, the water that filters across the glomerular capillary membrane of the kidney carries with it the solutes of plasma (Ref. 3).

(2) *Facilitated diffusion.* Facilitated diffusion is dependent upon the concentration gradient but does not obey simple diffusion laws. An example of facilitated diffusion is the penetration of sugars through the red cell membrane. There is evidence indicating that these are dissolved in water and inward passage thereby is facilitated (Ref. 3).

(3) *Active transport mechanisms.* These are not dependent upon diffusion and may even resist it. Sodium ions present in a nerve after an inpluse has moved along its course must be extruded to the resting exterior to restore the cell membrane to its normal resting state. These ions must be pumped out of the interior of the fiber, where the concentration is low, to the exterior, and into the extracellular fluid

where the concentration is much greater. This involves a mechanism similar to pumping water up a hill. A characteristic feature is that it can be blocked by metabolic inhibitors which interfere with enzyme activity. It can also be inhibited competitively by other substances which utilize the same type of transport mechanisms. Active transport often shows specificity for particular types of chemical structures. The transport mechanism can become saturated when the concentration of the substances exceeds a certain limit and ceases. Other examples of such active transport involving metabolic energy in addition to the extrusion of sodium ions by nerve or muscle are the secretion of hydrogen ions by the stomach, the reabsorption of glucose by the tubules of the kidney, and the secretion of penicillin by the tubules of the kidney. Active transport is often visualized in terms of carrier mechanisms. The carrier may itself be an ion with a charge opposite to that of the ion to be transported. Specific carriers are responsible for the absorption of glucose and amino acids by the intestines. There are at least two carrier mechanisms in the kidney. One is for the secretion of acid compounds, such as penicillin and phenol; the other is for secretion of basic compounds containing the quaternary ammonium group or amines. Both the acidic and the basic mechanisms are competitive, so that the transport of one substance can be blocked by an excess of another substance in the same group (Ref. 3).

(4) *Pinocytosis.* This is a type of transport mechanism that involves the movement of substances, of large aggregates of molecules, or of large particles across cell membranes such as are found in emulsions and suspensions. It is an entirely different type of transport mechanism from all the others encountered. The cells engulf small droplets of an extracellular fluid. Pinocytosis can be observed in ameobae and in tissue culture cells. This probably occurs in mammals, also. Its role is poorly understood, but it has been suggested that it might be responsible for the uptake (absorption) of protein in the gastrointestinal tract of infants or for the absorption of liquid droplets in the alveoli of the lungs. It is doubtful that it plays any role in the absorption of drugs in the oral cavity or pharynx (Ref. 3).

Bioavailability of a drug is a term used to define the rate and extent to which a drug reaches the site of action after administration. In its most general sense, bioavailability refers to all methods of administration of drugs, e.g., orally, subcutaneously, intravenously, etc., and to any site of action. In practice, the term is most frequently applied to the oral administration of drugs and to the determination of blood levels after administration (Refs. 3, 4, and 5).

Absorption of drugs through the lining of the mucous membranes of the mouth and throat is similar to that of the gastrointestinal tract. These membranes behave as lipoidal barriers for the passage of drugs. The rate of absorption is determined by the proportion of nonionized drug present at the pH of the mouth, or throat, which is about 6, and by the drug's lipid solubility. Nonionizable lipid-soluble compounds such as nitroglycerin and various steroids are readily absorbed through the oral mucosa. The buccal route is especially advantageous for the administration of certain drugs which are acid-labile and are rapidly metabolized by the liver, since the acidic stomach and the portal circulation which carriers them to the liver are bypassed. High molcular weight compounds such as proteins, for example insulin, are not appreciably absorbed and may be largely destroyed by digestive processes in the mouth. Certain workers (Ref. 3) have developed a buccal absorption test in which the subject's mouth is rinsed for 5 minutes with a buffered drug solution which is then expelled and analyzed. They found that absorption could be entirely accounted for by the lipid solubility of the undissociated molecules of a drug. For example, at pH 9.2 over 70 percent of a solution of amphetamine was absorbed, whereas, at pH 6, none was absorbed. Absorption increased linearly with the concentration of the drug. There was no selectivity in the absorption of optical isomers of amphetamine, suggesting that absorption occurs by diffusion rather than by active transport (Ref. 3).

It was formerly believed that only a few exceptional substances, such as alcohol, were absorbed from the stomach. It is now known that drugs which are weak acids are absorbed to an appreciable extent from the stomach. Aspirin is practically undissociated at a pH 1 and, therefore, absorbed from the stomach. However, it is not readily absorbed from the mouth. If the gastric contents are made alkaline with sodium bicarbonate, the aspirin is not absorbed. Bases are generally not absorbed from the stomach because they form salts with the hydrochloric acid and are ionized.

Cutaneous barriers are more easily traversed by bases of drugs such as local anesthetics, etc., than by their salts. The penetration of bases through cutaneous barriers, however, appears to be limited, and not comparable to that occurring through the epithelial cells of the mucosa in either quantity or rapidity. Salts of most drugs are poorly absorbed or not absorbed from the skin (Ref. 2). Absorption of local anesthetics from the mucous membranes may occur rapidly (Ref. 6). Resulting blood levels simulate those following slow intravenous injection. The resulting blood level depends upon the area exposed (the anatomic site), concentration, and the total quantity applied. Furthermore, salts of local anesthetic drugs are as readily absorbed as the bases by the mucous membranes and cause a blockade. The anesthetic effect on the mucous membranes persists for some time after application, unlike the cutaneous responses, which promptly disappear after the drug is wiped from the surface. Absorption from the mucous membranes varies with the type of mucous membrane. A product may act twice as long on the conjunctive as it does on the tip of the tongue (Ref. 7).

The dissimilarity in absorption of drugs from the skin and the mucous membranes can be explained by histologic differences of these two types of epithelial coverings. Epithelial cells differ from each other in having an inherent tendency to make extensive mutual contact by means of small branches without cytoplasmic continuity. This characteristic has been referred to by Farquhar and Palade (Ref. 2) as the macular adherence. The epidermis varies from 0.7 to 0.2 mm in thickness, but is entirely devoid of blood vessels. Presumably, it is nourished by capillaries in the underlying connective tissue. The tissue fluids pass from the capillaries into an extensive system of extracellular channels and into the malpighian layers by simple diffusion (Ref. 2).

The mucosal tissues differ from cutaneous epithelium in a number of ways. In the mucosa there is no apparent separation of the epithelium from the corium except for a subepithelial membrane. Mucous membranes are more permeable than skin because they have no cornified layer to form a uniform barrier. Recent studies have revealed the presence of innumerable fingerlike protrusions from the mucosal cells that interdigitate with similar structures of adjacent cells. This results in a substantial increase in the area of the cell membrane surface of the superficial oral mucosa. A greatly enlarged absorbing surface facilitates drug penetration. The projection of these

basal cell processes into the corium and the absence of capillary basement membrane likewise favor rapid absorption of drugs from the mucosa. These observations explain, to a great extent, the greater degree of absorption of drugs from the mucous membranes than from the skin (Ref. 2).

Studies on the absorption of drugs from the oral mucosa indicate that diffusion plays a dominant role in absorption and that the lipid-water solubility coefficients are less important considerations. Whether the mucus and saliva significantly enhance absorption from the mucous membranes by acting as a spreading factor has not been established. Likewise, the pH of these surfaces may influence absorption of drugs since mucus and saliva may favor liberation of the base from the salts. The base is the active form, and the form that penetrates the mucous membrane. The rapidity of absorption of local anesthetics from the mucous membrane varies with the mucous surface studied. Peak levels of local anesthetics are attained most quickly after application to the mucous membranes of the tracheobronchial tree, less quickly after the anesthetics are applied to the mucosa of the mouth and throat, and least quickly after gastric and esophageal instillation. Blood levels may rise quickly after instillation of a drug in the posterior urethra, particularly if the surface has been traumatized by instrumentation. No significant absorption occurs from the bladder. No significant quantities are absorbed from the unbroken skin (Refs. 2, 6, and 7).

Vasoconstrictors added to local anesthetics injected perineurally retard absorption. They may not influence blood levels when combined with drugs used topically. Clinicians who use topical anesthetics regularly realize that reactions occur more often after topical application than after perineural injection. The occasional user, however, is often not fully aware of the hazards of topical application and is the one who most often encounters difficulty. Some of these drugs are potent and cause severe and often fatal reactions when they are absorbed from the mucous membranes. The Panel therefore has placed certain of these in Category II from the standpoint of safety (Refs. 6 and 7).

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4. *Symptoms for which OTC oral health care ingredients are used in the mouth and throat*—a. *Sore throat.* "Sore throat" is a symptom with many manifestations and with numerous causes. The term generally denotes pain (particularly on swallowing), discomfort, burning, or a scratchy sensation of the mucous membranes of the oropharynx or hypopharynx or both. A person having the symptom and describing it to others may convey as many impressions of what is being experienced as the number of persons to whom the symptom is described. Since the term is a general one and nonspecific, various adjectives are used to attempt to define it more clearly or describe it more accurately. Such adjectives as "mild," "minor," or "severe" are often used to describe the degree of discomfort. Such terms as "minor throat irritations" and "throat irritations" are likewise used to describe a sore throat (Refs. 1 through 4).

Sore throat is, in most cases, a manifestation of some systemic, infectious, or moninfectious disease. The Panel finds that many currently marketed oral health care products with sore throat claims are related to the common cold. The Panel recognizes the accepted use of these products by the consumer for treating cold symptoms. However, sore throat may also herald the onset of a serious, possibly fatal disease. Various viral diseases, such as measles, chickenpox, smallpox, and poliomyelitis, often begin with symptoms of the common cold, influenza, or incipient pneumonia, and are often accompanied by rhinitis (runny nose), cough, nasal congestion, fever, and other symptoms. Sore throat may be a symptom of serious diseases caused by bacteria, such as diptheria, scarlet fever, Vincent's angina, oral gonorrhea, or diseases caused by other organisms, such as secondary syphilis. It may be an early manifestation of aplastic anemia, agranulocytosis, or acute leukemia. Sore throat may also be due to local causes, such as swallowing irritating foods or drugs or an accumulation of thick viscous secretions from nasal or pharyngeal infections (postnasal drip). It may be due to fungal infection, such as candidiasis, resulting from use of topical antibiotics. it may also be due to the inhalation of irritating fumes, such as smoke, of noxious gases such as chlorine, or to the ingestion of concentrated solutions of caustic chemicals. Sore throat due to streptococcal infections may be followed by rheumatic fever or acute glomerulo nephritis. The Panel emphasizes that sore throat, "mild" as it may be, may often be a symptom of a condition which is amenable neither to self-diagnosis nor to self-treatment (Refs. 1 through 6).

The severity of the discomfort caused by a sore throat often depends upon the psychological response of the individual to the condition and its implication, particularly in reference to an impending illness. A sore throat developing on the first day of a vacation may have a different psychological impact than one developing at the end of the vacation. Such an individual is usually the one who resorts to self-diagnosis and self-treatment to obtain a "quick cure."

The cause, the extent, and the type of process causing the sore throat are important considerations. A slight reddening of the pharyngeal membrane may cause a "scratching" or a burning sensation in some persons and no symptoms in others. A localized infection in the oropharynx or hypopharynx or both may often be symptomless though this is rare. A pharynx that appears fiery and red may cause only a minor discomfort in some individuals and little or no pain, while it may cause severe pain in others. The Panel emphasizes that the factors involved in causing the sore throat are often of more importance than the degree of discomfort experienced. A slightly infected throat may be accompanied by runny nose, runny eyes (tearing), sneezing, cough, muscle aches, pain, fever, and gastrointestinal disturbances indicative of some type of systemic disease, usually a viral infection and, in many cases, of the "common cold." In certain cases of sore throat, particularly those due to organisms such as *Streptococcus pyogenes*, patches of exudate are

scattered over the pharyngeal mucosa. These discrete individual areas are painful in some persons and painless in others. An inflammatory process characterized by diffuse reddening of the mucous membranes, sometimes with an edematous appearance, may be more than a superficial process in the mucosa of the pharynx. Close examination often reveals that it extends into the deeper structures of the pharynx and involves the submucosal structures or superficial layers of muscles, the anterior and posterior pillars, or the muscles of the posterior pharyngeal wall causing marked discomfort on swallowing. The pain may even be referred into the nasopharynx to the areas of the Eustachian tubes, where it may cause earache. In cases in which the tonsils have been removed, an inflammatory process with or without exudate may be present in the tonsillar fossa and cause discomfort and pain (Refs. 1 through 6).

Sore throat may be due to acutely or chronically inflamed tonsils. In some cases, the process may proceed to abscess formation. Peritonsillar abscesses cause considerable pain and discomfort and often require surgical intervention. On rare occasions, the enlargement of one tonsil, accompanied by pain, has been due to a tumorlike growth. Since the tonsils are composed of lymphoid tissue, they may become enlarged and cause varying degrees of discomfort in cases of leukemia, Hodgkin's disease, and other types of lymphomas. Exudate from infections in the paranasal sinuses passing from the nasopharynx into the oropharynx or hypopharynx may cause sore throat by acting as a foreign body. The discomfort disappears when the exudate is removed (Refs. 1 through 6).

Sore throat may be due to trauma from foreign bodies such as glass, fish bones, or sharp pieces of bone that scratch the mucosa during swallowing when ingested with food. It may follow surgical procedures, such as tonsillectomy, biopsy, intubation, insertion of pharyngeal tubes, nasogastric airways, mouth gags, dental manipulations when the mouth is opened too widely from use of mouth gags, etc.

The Panel has gone to some length to enumerate these numerous causes and manifestations of sore throat to emphasize that sore throat is merely a symptom. In most cases, it is due to a self-limiting benign condition that recedes without treatment. In other cases, it cannot be ignored and medical advice must be sought. The Panel recommends that the term "sore throat" be used without qualification, as far as indications are concerned, as to its etiology and severity. However, it should be qualified by adequate warnings in the labeling.

Sore throat due to trauma is self-limiting and requires time for the healing process to occur. Anesthetic/analgesic-containing oral health care products may be helpful in these cases. Sore throat due to the accumulation of exudates may respond to agents that liquefy the exudate, or act as debriding agents and remove the exudates from the muccous membranes. Mucoid exudates that collect and cause discomfort can be removed by using sprays, or by irrigation with alkaline solutions. Pain can be relieved by applying topical anesthetics/analgesics in the form of sprays or in the form of lozenges which provide a continuous coating over an inflamed surface. The effectiveness of gargles in relieving discomfort due to sore throat is questionable because during the act of gargling the anterior pillars of the fauces approximate, the tongue rises, and the walls of the pharynx approximate. The action of the air stream prevents the access of fluid to the posterior pharyngeal wall. The various types of ingredients mentioned above for the relief of sore throat will be discussed individually later in this document.

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b. *Sore mouth.* "Sore mouth" is a symptom which has many causes and which exhibits many manifestations. The term is used in this document to denote discomfort, a burning or scratchy sensation, or pain of the mucous membranes and other structures in the oral cavity. It may be generalized or localized. When localized it may involve the hard palate, soft palate, tongue, sublingual structures, frenulum, the buccal mucous membranes and the membranes on the inner side of the lip and the gingivae (gums). The Panel is not considering symptoms involving the teeth, periodontal structure, and gums since these have been reviewed by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products.

The causes of sore mouth are numerous and varied and may be of a serious nature. Most of them are not amenable to self-diagnosis and self-treatment. As is the case with sore throat, sore mouth may be due to local causes or it may be a manifestation of a serious systemic disease. Sore mouth may be caused by trauma, burns, infections, neoplasia, metabolic disorders, developmental disorders, systemic diseases, and drug reactions. In addition, recurrent oral ulceration may occur including minor aphthous ulcer, major aphthous ulcer, and herpetiform ulcer (Ref. 1). The various causes of sore mouth are discussed in detail below to illustrate that few can be treated with OTC products. The following is an enumeration and discussion of the more obvious causes of sore mouth.

Trauma is one of the most common causes of sore mouth. It may result from injury from toothbrushing, from dentures, of from lacerations or abrasions from eating hard foods. Trauma may also be due to accidents from blunt force and other causes. The Panel is considering only minor trauma in this discussion and is excluding major trauma which occurs as a result of accidents in which there may be soft tissue injury and damage to teeth and jaws.

Trauma from the above causes may be mainfested by traumatic ulcers of the oral mucosa. Typically, these ulcers are linear with a gray, fibrinous exudate on the surface. Chronic ulcers of this type may show a considerable amount of induration of the surrounding tissue and may simulate squamous cell carcinoma. They may be difficult to distinguish from the latter on examination. Treatment with OTC products is usually not necessary since healing will occur following removal of the source of the trauma, e.g., dentures. A physician or dentist should be consulted when any ulcer persists for longer than 1 week.

Sore mouth may be due to chemical burns of the oral mucosa. Many chemicals and drugs may be caustic and cause burns in the mouth. Acids, antiseptics, kerosene, and numerous household substances may be ingested accidently and cause burns. There is cogulation of the surface epithelium, creating a necrotic slough with a white appearance. Healing usually occurs spontaneously without the use of drugs within 7 to 10 days. Some drugs may also cause burns. Aspirin (Acetylsalicyclic acid), phenol, trichloracetic acid, silver nitrate, and sodium perborate are examples of some that may do so.

Thermal burns of the oral mucosa are also a common cause of sore mouth. these arise from the accidental ingestion of hot foods and beverages. The anterior third of the tongue and the palate are the most common burn sites. Most of these burns are usually of little consequence and of relatively short duration. Burns may also result from inhaling flames, smoke, chemical fumes, and irritating gases, and may cause slough of the oral and pharyngeal mucosa. Fumes from ammonia, hydrochloric acid, chlorine, and other industrial chemicals may also cause burns of a similar type.

Sore mouth may be due to infections. Bacterial, viral, and fungal infections can occur in the oral cavity as well as in the throat (Ref. 2). Few of these are amenable to self-diagnosis and treatment with OTC oral health care products. The majority require diagnosis and treatment by a physician or dentist. Such infections are as follows:

(1) *Acute necrotizing ulcerative gingivitis (ANUG or NUG) (Vincent's infection).* This is one of the most common infections of the oral cavity and throat. It is characterized by the presence of interdental ulcers covered with a grayish exudate which bleed easily. Tenderness, malodor, fever, and malaise may be associated with the infection (Refs. 3, 4, and 5). Less commonly, a gingival flap overlying an erupting tooth, the palatal and buccal mucosa, or the oropharynx (Vincent's angina) may be affected. Antibiotics are usually necessary to relieve symptoms or eradicate the infections. The services of a dentist or physician are necessary for diagnosis and treatment.

(2) *Gonococcal lesions of the mouth.* These occur following orogenital contact (Ref. 6). The diagnosis and appropriate treatment can only be made by a physician.

(3) *Tuberculous lesions.* These are usually secondary to pulmonary tuberculosis, although it is possible that they can be of primary origin (Ref. 7). This type of infection is characterized by a chronic ulcer of the tongue or buccal mucosa. Self-diagnosis and self-treatment of such lesions is obviously not possible, and a physician must be consulted.

(4) *Syphilis.* Syphilis is a systemic disease caused by *Treponema pallidum.* It is most frequently acquired through sexual intercourse. An ulcer or primary lesion, known as a chancre, appears at the portal of entry. Syphilis is a systemic disease and occurs in three stages. Primary, secondary, and tertiary syphilitic lesions can occur in the oral cavity and result in a sore mouth (Ref. 8).

About 6 weeks after the chancre first appears, the secondary stage becomes manifest. It is characterized by a sore throat, and possibly sore mouth due to mucous patches. Generalized lymph node enlargement and skin rashes may also be present. The mucous patches are gray and translucent and are highly infective. Split papules at the angles of the mouth may occur that resemble angular cheilitis.

The tertiary stage of syphilis is characterized by the presence of the gumma which may occur intraorally as well as on other parts of the body. A gumma is usually characterized by a midline, punched-out lesion of the palate or tongue. Obviously this disease is not amenable to self-diagnosis and treatment with OTC oral health care products.

(5) *Primary herpetic stomatitis.* This disease is due to herpes simplex virus and is characterized by blisters on the cheeks, tongue, palate, floor of the mouth, and gingivae. The gingivae are frequently bright red, swollen, and bleed easily. These blisters rupture, leaving grayish-white ulcers with reddish borders which are painful. The infection is accompanied by fever. It is commonly seen in young children, and they may refuse to eat and drink because of pain. This type of infection requires expert care rendered by a dentist or physician.

(6) *Secondary or recurrent herpetic infections.* These infections are also due to herpes simplex virus. They are characterized by ulcerations which most commonly involve the hard palate. They may also appear on the lips. They cause discomfort characterized by a burning sensation or pain.

(7) *Herpangina.* This type of infection is caused by the Coxsackie group A virus. It is a relatively common disease of young children which occurs in mild epidemics towards the end of summer. Fever, intestinal upset, headache, and sore throat usually precede the appearance of tiny vesicles on the soft palate and pharynx. These ruptures leaving small ulcers with erythematous borders which also cause a burning sensation or pain. This type of infection requires professional attention and should be treated by a physician or dentist.

(8) *Candidiasis.* This is a fungal infection which is one of the most common afflictions of the oral cavity (Ref. 9). There are various strains of candida, but *Candida albicans* is still the most common causative organism of this type of infection (Ref. 10)

Infections due to candida may be either acute or chronic. The acute forms include acute pseudomembranous candidiasis (thrush) and acute atrophic candidiasis (Ref. 11). The chronic forms include chronic hyperplastic candidiasis and chronic atrophic candidiasis. Oral candidiasis is characterized by the presence of white plaques, or diffuse erythematous areas in the mouth. Infections due to candida can only be diagnosed by a physician or dentist using laboratory methods. Obviously candidal infections are not amenable to self-treatment with OTC oral health care products.

Angular cheilitis is an infection associated with denture stomatitis. Cohen (Ref. 9) states that the lesions of angular cheilitis are frequently infected by *Candida albicans* or coagulase-positive *Staphylococcus aureus.* In some cases both candida and staphylococcus are involved. The infection is characterized by fissures at the angles of the mouth that often heal without local medication. Obviously, the aformentioned infections are not amenable to self-treatment with OTC oral health care products.

There are several types of recurrent oral ulcerations. Among these are aphthous stomatitis, also know as recurrent aphthous stomatitis (RAS), and Behcet's syndrome. Aphthous stomatitis is not an uncommon cause of sore mouth. Lehner has applied the term "recurrent oral ulceration" to three varieties of recurrent oral ulcers (Ref. 1): minor aphthous ulcer (Recurrent aphthae of Mikulicz and Kummel, 1898) (Ref. 12), major aphthous ulcer (Periadenitis mucosa necrotica recurrens) (Ref. 13), and herpetiform ulcers (Ref. 14).

The minor and major aphthous ulcers are the most common of the three varieties. Both the minor and major aphthous ulcers are found in aphthous stomatitis and Behcet's syndrome (Ref. 15). The present evidence favors an immunological cause for both RAS and Behcet's syndrome.

These ulcerations result in various degrees of ulcers depending on their

location and extent in the mouth. They require diagnosis and treatment by a physician or dentist and are not amenable to OTC therapy.

Sore mouth may be an early symptom of oral cancer or other malignant lesions. Malignant lesions may make their first appearance as seemingly innocuous ulcerations or plaques such as leukoplakia. The lesion persists and enlarges. It may or may not be painful. Any ulceration or growth in the mouth, however small, that persists for more than several weeks should be examined by a dentist or physician. Many oral cancers are discovered by dentists. The Panel emphasizes that sore mouth may denote the presence of a serious lesion.

Anatomic aberrations due to developmental defects can result in sore mouth. Fissured or plicated tongue and erythema migrans (geographic tongue) can result in mouth soreness. Diagnosis and treatment of the disorder require the advice of a dentist or physician knowledgeable about oral diseases. Self-treatment with OTC products is not feasible.

Sore mouth may be a manifestation of certain blood dyscrasias. Blood dyscrasias include certain types of anemias (e.g., pernicious and aplastic anemia), the leukemias, agranulocytosis, and other leukopenias. These diseases are characterized by white cell deficiency and lower the resistance of the tissues and predispose to infections of the mouth which cause pain and soreness. In some anemias there is a loss of papillae on the dorsum of the tongue which induces soreness on the tongue. Lesions caused by these diseases can only be recognized and treated by a physician knowledgeable in hematology. None is amenable to self-treatment with OTC products.

Some systemic diseases are accompanied by lesions in the oral cavity that cause soreness or pain. Eruptive fevers, such as scarlet fever, smallpox, measles, and chicken pox, may cause oral lesions which cause sore mouth. The vesiculobullous diseases and certain generalized skin diseases, such as lichen planus, may also cause oral ulcers and the patient may complain of sore mouth. Obviously these diseases are not amenable to self-diagnosis, and the oral lesions are not amenable to self-treatment with OTC products.

Metabolic disorders such as chronic renal failure are characterized in their advanced stages by a rising blood urea and the clinical picture of uremia. Release of urea into the mouth via the saliva may cause stomatitis accompanied by sore mouth.

Diabetic patients are prone to develop sore mouth due to stomatitis because of the lowered resistance to infection. Self-treatment with OTC products may delay diagnosis, and the disease may progress to a serious state.

Deficiencies of certain vitamins such as vitamins C and $B_{12}$, minerals, and trace metals can result in sore mouth. Obviously none of these is amenable to self-diagnosis or treatment with OTC oral health care products.

Some drugs may induce systemic hypersensitivity reactions which are manifested by lesions in the mouth (stomatitis medicamentosa) and cause soreness in most patients. Some drugs used locally in the mouth can cause contact allergy (stomatitis venenata). Patients with stomatitis medicamentosa and stomatitis venenata usually complain of sore mouth. Such lesions are not amenable to self-diagnosis and treatment with OTC products.

It is obvious from the foregoing discussion of conditions that cause sore mouth that many are of a serious nature and rare and that, when compared to sore throat, the number that can be self-diagnosed and treated with OTC products is relatively small. Yet, sore mouth is common and occurs as frequently as if not more often than sore throat. In most cases it is due to minor ulcerations and other benign conditions that are self-limited and last only short periods of time. Therefore, there is ample justification for using OTC oral health care products for treating sore mouth. The anesthetics/analgesics offer temporary relief of pain and can be used as adjuncts to therapeutic regimens outlined by physicians in conditions where professional care is necessary. Debriding agents and expectorants may aid in the relief of soreness by facilitating removal of exudates which often coat these lesions. Demulcents and astringents may aid in relief of discomfort by providing a protective coating over a lesion, thereby reducing irritation due to external stimuli. As is the case with sore thorat, there is little if any evidence from controlled studies that the topical application of antiseptics is of any benefit in relieving these symptoms.

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c. *Cough.* Cough is a protective mechanism designed primarily to free the upper and lower respiratory tracts of foreign objects, secretions, pus, and other materials. Ingredients that suppress cough are called antitussives. Cough and antitussives have been considered by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products because antitussives generally act systemically and are administered orally, parenterally, and by other routes. However, receptors that incite cough are found in the hypopharynx (laryngopharynx), and the possibility that they can be suppressed by topically acting drugs should be given consideration. The Panel, therefore, is including a discussion of cough and its suppression since there is a possibility that some of the ingredients evaluated may depress the pharyngeal receptors

and act as antitussives by a local action (Refs. 1, 2, and 3).

Coughing is produced by the rapid expulsion of air from the lung at high velocity following a deep inspiration and immediate voluntary closure of the glottis which is, in turn, followed by a sudden opening of the glottis and by a rapid forced expiration. Sounds of varying intensity and pitch are produced, depending upon the rate of flow of the exhaled gas, the total volume expelled, the tension on the vocal cords, and other factors that are responsible for the vibrations of the air waves that are interpreted as sound. Impulses that initiate the cough reflex may arise from many areas both within and without the respiratory tract (Refs. 1, 2, and 3).

Normally, coughing is produced by stimulation of sensory receptors of the glossopharyngeal and vagus nerves distributed in the mucous membranes of the lower pharynx, larynx, trachea, lung, pleura, and other areas of the respiratory tract. Stimulation of these receptors can be initiated by inflammatory processes, edema, chemical irritation, the presence of retained secretions, or foreign material blocking the upper and lower airways. Localized narrowing of the air passages may play an important role in stimulating receptors that induce the cough reflex. The act of coughing is coordinated by a group of neurons in the medulla called the cough center. These neurons can be depressed by certain drugs, particularly the central nervous system depressants such as the narcotics. Their activity can also be enhanced by certain chemicals and toxins, e.g., pertussis. Cough, in most instances, is under a considerable degree of voluntary control and can be initiated and self-suppressed at will within certain limits. Cough is active as a protective mechanism in healthy individuals, as well as those who are ill, for clearing the airway of any obstructing mucous secretions, or inhaled or aspirated foreign material.

The majority of medications that suppress coughing exert their effects systemically, although it is possible that some medications act locally as topical anesthetics, or by reducing inflammation or by decreasing edema. The Panel finds that the instances where this occurs are relatively uncommon. Preparations acting systemically are administered by mouth in the form of tablets, syrups, elixirs, or lozenges. Since the lower portion of the oropharynx and the hypopharynx are supplied by the ninth (glossopharyngeal) and tenth (vagus) nerves, it is possible for stimulation in these areas to induce cough. Cough originating by such local stimulation can be suppressed by topically acting agents such as anesthetics, decongestants, or anti-inflammatory agents. These can be administered topically in the form of lozenges or sprays. As far as this Panel is concerned, their action is local and not systemic. The Panel believes, however, that in the majority of instances stimuli that incite cough are widespread in the respiratory tract and only respond to systemically acting antitussives (Refs. 1 and 3).

Cough is frequently the apparent symptom of a wide variety of pathologic conditions, ranging from mild, self-limiting conditions to a serious and even fatal illness. In many cases, it can be tiring and debilitating, and its suppression is desirable. However, the cough reflex should not be suppressed indiscriminately, because it is important in preserving the function of the lung by maintaining an open airway (Refs. 3 and 4).

The "irritative cough" associated with self-limiting pharyngeal infections is usually viral in origin. It may also follow the inhalation of irritant gases, smoke, or dusts. The manifestations of these conditions are usually associated with a dry, hacking, nonproductive cough in which no sputum is expectorated. This type of cough lends itself to rational self-medication with systemically acting OTC preparations and does not ordinarily respond to products that act locally. On the other hand, secretions from "postnasal drip" exudates from inflammatory conditions in the nose and throat may incite cough receptors in an already irritated or inflamed throat and induce cough. The removal of these secretions temporarily relieves the cough. OTC preparations that facilitate removal of these secretions may relieve this type of cough. Drugs, such as narcotics and dextromethorphan that are systemically acting antitussives, exert no significant local effect and do not come under the purview of this Panel.

Any cough which becomes progressively worse after 7 days should be investigated by a physician to exclude the presence of an underlying, potentially serious, respiratory disease (Refs. 1 through 4).

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5. *Dosage forms of oral health care products.* All the ingredients reviewed by the Panel are applied to the surface of the mucous membranes of the mouth and throat to achieve their therapeutic effects by means of surface or superficial penetration. The therapeutic effect is a local one due to direct action on the structures beneath the mucous membrances. Since mucous membranes are effective absorbing surface, systemic actions frequently develop when drugs are applied topically to their surfaces. The topical route is often utilized to obtain systemic effects. The quantity of and rapidity of absorption of a particular drug through a mucous membrane may vary widely in different areas of the body. Absorption through the mucosa of the mouth and pharynx occurs readily. Pathologic changes in the mucous membranes may impede absorption of drugs and chemicals. The oral and pharyngeal mucosa is generally sensitive to and irritated by long-lasting drugs that remain in contact with the mucosa for extended periods of time (Refs. 1, 2, and 3).

Ingredients are applied to the mucous membranes of the mouth and throat by use of drops or powders, by gargling, rinsing, irrigating, swabbing, or spraying, or by slowly releasing a film of a drug over a surface by the use of lozenges. The use of ointments in the oral cavity is generally impractical due to their viscosity and difficulty in application. Lotions are also not recommended for use in the oral cavity. Combining a drug with a demulcent which adheres to a mucous membrane may prolong its contact with that membrane. The duration of contact of an ingredient depends on its chemical nature, viscosity, its reactivity with saliva and mucus, and its mode of formulation.

Washing out the oral cavity can be accomplished by rinsing or gargling. The duration of contract of a drug after rinsing, gargling, and irrigation with aqueous solutions is generally brief, and in most cases the therapeutic effect is of short duration unless the preparation is formulated with ingredients that prolong contact.

Sprays consist of hand-operated bulb-type nebulizers or aerosols. The nozzle of an aerosol spray should be calibrated so that the dosage can be metered in terms of seconds of use or the duration of the time of delivery. Dosage of drugs

from hand sprays can be calibrated according to the number of times a bulb is squeezed or the duration in terms of the time of delivery of an aerosol. The particle size of a droplet from a spray should be uniform and between 30 and 100 um in diameter. Otherwise baffling occurs, or the droplets pass into the lung and the spray does not reach the surface for which it is intended (Ref. 4).

Swabbing may permit more prolonged topical contact of an ingredient, particularly when combined with a demulcent to prolong contact. It is also believed that swabbing, even if done very gently, may produce some abrasions of the mucosa and by doing so may increase the absorption of an ingredient. Theoretically, the contact of an agent would be the same, regardless whether it is applied by spray or swab (with the exception mentioned above). The germicidal action of topical antiseptic antimicrobial agents is confined to the surface to which the drug is applied and to the debrided tissues. They may not be effective if contact is brief; however, this depends on many factors like adherence, the vehicle, etc. Living cells resist the penetration of effective concentrations of antimicrobial agents (Ref. 5).

Topical anesthetics penetrate the mucous membranes and pass into the nerve receptors in the mucosa where they may remain for a period of time depending upon their chemical and physical properties, such as lipid solubility, protein-binding capacity, and molecular structure to exert a sustained effect.

Mucosal surfaces that do not normally come into contact with water are generally irritated by it since water is not isotonic (osmotic irritation). This irritation can be avoided by using isotonic solutions (0.9 percent) of sodium chloride. Solutions in oil are also used to avoid osmotic irritation. Their immiscibility with the moisture of the mucosa prevents direct contact with the cells, and their actions, therefore, are slower but generally more prolonged. Oils, however, are undesirable since they may be aspirated and overuse may cause pulmonary irritation and fibrosis. Ointments make poorer contact with a mucous surface because viscosity limits their spread (Ref. 5).

The mouth and throat are usually treated by use of sprays, swabbing, irrigation, or the use of lozenges. The Panel is doubtful of the effects of gargling for treating symptoms affecting the throat. Medication in a gargle will not reach the throat unless the liquid is swallowed. The airstream in gargling might help to expel mucus, similar to clearing the throat. This topic is described in more detail below.

Nose drops, sprays, and other OTC preparations instilled into the nose pass into the pharynx and may exert a therapeutic effect in some cases and an adverse effect in others. For this reason a discussion of the nasal muscosa is mentioned here (Ref. 5). The nasal mucosa differs from that of the mouth and oropharynx in its response to drugs. Hypotonic and astringent solutions are less irritating than hypertonic solutions. Burning and other disagreeable sensations in the throat may follow the use of nose drops. Absorption in the nose occurs readily so that the local effects of drugs may occur quickly (Ref. 5).

The Panel has considered the various modes of application of topical products to be used in the oral cavity. Some examples of methods of application generally appearing on the labeling include "gargle freely," "spray freely," etc. The proposed labeling denotes the methods of application that are indicated for the various active ingredients, the dosage form, and the type of vehicle employed. Some preparations may be used in several different ways, as for example in the form of sprays, incorporated in the form of a lozenge, or prepared in the form of a rinse (Ref. 5). The accepted technique and directions for use appear in the labeling of the appropriate ingredient or combination statements discussed elsewhere in this document.

a. *Gargles and mouthwashes.* A gargle is a fluid, usually flavored or medicated or both, but not necessarily so, which is intended to be used to rinse or bathe the posterior part of the oral cavity, with the additional intent to expel mucus from the throat. The gargle solution does not reach the throat unless it is swallowed. Gargling is accomplished by taking the fluid into the mouth and forcing expired air through it, while the head is tilted backward (Ref. 6). A gargle is intended for cleansing the throat, treating a diseased state, or relieving symptoms due to a diseased state of the throat. A mouthwash, or mouth rinse, also known as a collutorium, which may or may not be medicated or flavored, is a fluid used for cleaning the mouth or treating diseased states of the mucous membranes of the mouth. Actually the terms "gargle," "mouthwash," and "mouth rinse" merely denote how fluids are used in the oral cavity and give no indication as to what benefits may result from their use (Refs. 6 and 7).

Most mouthwashes are aqueous or water-alcoholic solutions in which are incorporated active therapeutic ingredients, pleasant-tasting flavorants, pleasant odoriferous materials, and various pharmaceutical necessities. The active ingredients present in these solutions are varied (Ref. 8).

The ideal solution used for a gargle, mouthwash, or mouth rinse should be one that is noninjurious to the normal tissues of the mouth and throat. It should be stable, composed of ingredients that remain in contact for the time required to exert the claimed therapeutic effect, and not be absorbed by the mucous membranes. It should be easily washed from the mucous membranes. It should be easily washed from the mucous membranes when the desired effect has been obtained and there is no longer any need for the drug to be in contact with the tissues. It should be nonirritating and nonsensitizing to tissues, pleasant tasting, pleasant smelling, and nontoxic if swallowed and absorbed from the gastrointestinal tract.

Unfortunately, the terms "mouthwashes" and "rinses" do not accurately define such preparations on the basis of composition, nor do they differentiate between therapeutic or cosmetic uses. Most mouthwashes are used for cosmetic purposes and consist of liquids with pleasant odors and tastes to rinse out the mouth.

The Panel regards gargles, mouthwashes, and mouth rinses that contain ingredients used for cleansing purposes, flavorings, or odorants, particularly those that are used on a regular basis such as one or more times daily and are not used to treat symptoms of a disease state of the mouth and throat, as cosmetics. The Panel emphasizes that OTC oral health care products for which a medicinal claim is made should be used only occasionally and for short-term therapy. This time limit should be designated on the labeling. The Panel does not regard oral health care products appropriate for use proplylactically to prevent the development of symptoms or disease states of the mouth and throat. The Panel recommends that any medicinal claims for "prevention" not be allowed.

The value of gargling in the treatment of sore throat is questionable (Refs. 8 and 9). This has been the subject of discussion in the literature for many years (Ref. 10). Tests performed with dyes and colored powders, such as charcoal black or radiopaque substances, followed by visualization by roentgenogram support the contention that in most cases, gargles may reach the anterior pillars but not the posterior pharyngeal wall or the posterior pillar (Ref. 10). They do not necessarily

establish physical contact of a medicine with a diseased surface of the pharynx. Contact is made in the oral cavity (Refs. 5, 8, and 12).

It is argued that many solutions used for gargling contain detergents that lower surface tension and enhance the ability of the liquid to penetrate into areas not accessible to water. This property facilitates penetration to convoluted areas of the tongue, mouth, and throat, aiding in debridement of these areas. It is also claimed that the physical act of gargling also creates an aerosol type of dispersion which aids in the spread of the solution and its ingredients throughout the mouth and throat.

It is the feeling of the Panel that these differences in conclusions drawn from studies concerning the effectiveness of gargles for use in the throat are due to numerous variable factors that enter into a study. During the act of gargling, the anterior pillars of the fauces approximate, the tongue rises, and the walls of the pharynx approximate. The action of the airstream prevents the access of fluid to the posterior pharyngeal wall. The gargle does not reach the throat. The airstream is directed away from the throat, preventing fluid from running back.

It is the consensus of the Panel that sprays are more effective for use in the throat, and the Panel recommends their use for products intended to reach the pharyngeal structures (Ref. 8). (See part II. paragraph B.5. below—Dosage forms of oral health care products.)

The absurd notion that antimicrobial agents in gargles, mouthwashers, and mouth rinses are necessary for daily cleansing of the mouth and throat is based upon tradition, promotional appeal by manufacturers, and misunderstandings concerning their effectiveness and safety rather than on well-documented facts (Ref. 11). The introduction of anti-infective drugs such as the chemotherapeutic agents, antibiotics, and other drugs possessing selective toxicity for a particular micoorganism or class of pathogenic microorganisms without harming the cells of the host has been responsible for relegating antiseptics for use in the mouth and throat into obsolescense. The selection of the proper antimicrobial agents manifesting selective toxicity for an offending organism can only be made by a practitioner of medicine or dentistry. The majority are administered systemically and not topically.

The Panel has reviewed and agrees with the findings of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group (DESI), which pertain to uses of mouthwashes and gargle preparations. In publishing a proposed statement of policy in the **Federal Register** of August 4, 1970 (35 FR 12411), the Commissioner of Food and Drugs stated:

> that there is a lack of substantial evidence that those preparations are effective for any of their labeled claims which relate to antimicrobial, antiseptic, germicidal, and analgesic uses.
>
> In addition to mouthwash and gargle preparations for which new-drug applications are in effect, there are many similar products on the market. The Food and Drug Administration has surveyed the labeling of such products and finds that many of them make direct or implied claims for benefit relating to antimircorbial, antiseptic, germicidal, or analgesic effects. Available information has been reviewed and has not been found to substantiate such claims.
>
> (c) The Administration will not object to labeling of a mouthwash, mouth freshner, or gargle preparation which offers it for such use as an aromatic mouth freshener (provided the product contains aromatic ingredients); as a refreshing mouth rinse; as an aid to daily care of the mouth, and for causing the mouth to feel clean. The label declaration or implication that an ingredient of such an article is active, when this is used to imply that the article has a prophylactic or therapeutic effect, may cause the article to be misbranded. However, an ingredient may continue to be listed on the label if it does in fact contribute to the nonprophylactic and nontherapeutic and usefulness of the article (e.g., wetting agent, foaming agent).

It is obvious that these claims are cosmetic and not therapeutic and that both the NAS–NRC study group and FDA regard mouthwashes as cosmetics. The Panel, from its evaluation of ingredients in oral health care products discussed below, likewise concludes that there are few, if any, indications justifiying the use of OTC mouthwashes, mouth rinses, and gargles containing antimicrobial agents for self-medication or for oral health care by lay consumers.

b. *Lozenges and gums.* Lozenges or troches, as they are sometimes called, are circular or oblong in shape. They are made by cutting, punching, or molding a flavored mass consisting of sugars, mucilages, gums, or bases of fruits, in which active therapeutic ingredients are incorporated. They are intended to be sucked, gradually releasing drugs into the saliva to act topically in the mouth and throat. They are made of varying consistencies depending upon the intended dissolution rate that is required to liberate the desired quantity of drug for the indicated therapeutic purpose (Ref. 13).

The therapeutic effectiveness of lozenges is difficult to evaluate because many variable factors may alter their performance during the conditions of use. Meaningful data from well-controlled studies on the effectiveness of lozenges are lacking because such data are difficult to obtain in patients. The composition, stability, consistency, size, rate of dissolution, taste, odor, and appearance of a lozenge are all important factors that enter into determining their effectiveness. There is no set of "average" conditions under which the effectiveness of a lozenge can be determined. The size and area of the mouth and throat, the surface area the drug is intended to cover, and the amount, the pH, and viscosity of the saliva being secreted all vary widely from one individual to the next and even in the same individual from moment to moment, modifying the action of the ingredients in a lozenge. Generally, a given dose in milligrams of each ingredient is incorporated in a single lozenge. The cohesion, the ease of aborption by the mucous membrane, the stability of drugs released from a lozenge, and the cause and type of lesion being treated are also important considerations. Drugs that are not soluble and not easily absorbed by the oral and pharyngeal mucous membranes pass into the stomach and may be absorbed there, acting systemically. The duration of action of drugs released from lozenges is generally short-lived and disappears as soon as the drugs are washed away by the salvia unless they penetrate cells and bind with proteins and other cellular constituents or are incorporated with demulcents that are tenacious and not easily washed away by the saliva. Their cohesion to the mucous membranes is generally unpredictable and of short duration, particularly if they are water soluble. Thus, in many cases if lozenges are to be effective they must be used frequently, usually in succession. As one dissolves, another must replace it if the active ingredients are to be of benefit.

Claims are made by some manufacturers that the effectiveness of some drugs released from lozenges may be two- or three-fold longer than the life of the lozenge. In some cases the Panel doubts that this claim can be made because the effect of the active ingredient is of short duration. The Panel doubts that benzocaine released from a lozenge can produce anesthesia for 3 or 4 hours when it finds that aqueous solutions of the same ingredient afford relief for less than 30 minutes.

Lozenges for use in the mouth and throat usually contain antimicrobial agents, local anesthetics, astringents, expectorants, demulcents, decongestants, debriding agents, or combinations of these.

The oropharyngeal symptoms which lozenges are intended to relieve are commonly due to local infection, ulcerations, congestion, and occasionally to irritation from drying of the mucosa, due to mouth breathing or from smoking. Most local infections, particularly in the throat, are viral or bacterial in origin. They are likely to resolve spontaneously. They can also be manifestations or prodromal symptoms of serious illness, particularly those in the throat, as is the case in various fevers, systemic viral infections, agranulocytosis, leukemia, diabetes, uremia, dehydration, and other such conditions. Infections can also be of fungal origin and respond to local treatment. However, the expertise and advice of a physician is required in such situations. OTC products are not appropriate for treatment in these conditions. They may, however, give symptomatic relief.

There is no evidence based on well-controlled clinical studies to support the effectiveness of lozenges which contain antimicrobial agents for OTC use. It is doubtful that they reach the microorganisms in the infected tissues. Effective broad-spectrum antiseptic agents not only kill the microorganisms but also damage the host cell. The Panel feels that such agents may do more harm than good. Furthermore, dilution by the flow of saliva and the poor contact with infected tissue make the use of antimicrobial ingredients in lozenges an inefficient method of applying such drugs locally. The medicines, as a rule, fail to reach infections in the furrows of the tongue, tonsillar crypts, and other inaccessible areas. Even if they do reach the areas, long-term clinical use attests to the fact that they are of dubious value in overcoming infections. A low concentration of an antimicrobial agent in the mouth can also encourage overgrowth of resistent bacterial organisms and fungal agents, such as oral candida, perhaps by altering the natural flora in the mouth (Ref. 14). If an antimicrobial agent is necessary to combat an infection such as a streptococcal sore throat, then one with specific activity, such as pencillin, should be taken orally or given parenterally and used under the advice of a physician. Though certain antimicrobial agents in lozenges may be helpful in treating certain ulcerative conditions, drugs that are effective systemically are preferred to those applied locally. Some antiseptics may irritate the mucous membranes and, likewise, some drugs, when applied locally, may also cause sensitization and at a later date cause hypersensitivity reactions if there is reexposure to the agent.

Lozenges containing local anesthetics often temporarily help relieve soreness in the mouth and throat and are worth using when this symptom is troublesome, provided the agent is able to reach the affected site and penetrate through the mucous membranes to exert its action on pain receptors. Benzocaine is one of the most widely used drugs for this purpose. Benzocaine can sensitize, but is seldom known to do so when used in lozenges. When patients are already sensitized to a drug after topical use on the skin or systemically, lozenges containing that drug can cause local hypersensitivity reactions when applied to a mucous membrane.

Aromatic flavorants or odiferous substances may increase the flow of saliva. Their vapor, if they are volatile, may produce a sensation which partially masks minor pharyngeal and nasal discomfort. Menthol, for example, stimulates receptors for cold, thereby producing the sensation of coldness which temporarily masks the pain. Menthol has a local anesthetic effect with a mean duration of 1.5 minutes and a mean latency period of 0.16 minutes (Refs. 15 and 16).

Demulcents incorporated in lozenges may relieve discomfort by coating irritated or inflamed mucous membranes and acting as protectants. Astringents incorporated in lozenges may act as protectants by coagulating proteins and may relieve symptoms. Debriding agents and expectorants, when incorporated in lozenges, may aid in the removal of phlegm, mucus, and debris, thereby relieving pain and discomfort. Decongestants incorporated in lozenges may relieve symptoms by shrinking mucous membranes and relieving congestion and by reducing swelling which is stimulating pain receptors.

The stability of ingredients and their chemical interaction with the "inactive" ingredients of a lozenge or a troche is of some concern to the panel. In one particular study, a formulation containing benzocaine was found to have lost half strength after 6 months in an unopened container (Ref. 17). Aspirin in certain formulations is hydrolyzed, and the odor of acetic acid is predominant when the container is opened. Phenol may be oxidized to quinones and be rendered ineffective. The shelf life of a lozenge, also, is of concern to the Panel. Not only does the Panel feel that the tenets of good manufacturing procedures be rigorously followed, but also that the shelf life of a product be indicated together with conditions of storage and other pertinent environmental factors.

Aspirin is incorporated in chewing gum supposedly to provide a topical action. In most cases the use of the gum is intended for slow release.

The Panel feels that the weight of the drug in milligrams per lozenge should be stated along with the total weight of the lozenge so that the consumers have all data and all facts pertaining to the concentration of drug in the formulation.

The following is a brief summary of the use of lozenges. Local anesthetic-containing lozenges may temporarily alleviate discomfort and soreness of the throat and are worth using when these symptoms are present. Astringents and demulcents may act as protectants and are also worth using. Debriding agents in lozenges alleviate discomfort by removing phlegm, mucus, and other debris. Effective expectorants may do likewise. Decongestants in lozenges decrease congestion of mucous membranes and alleviate discomfort due to inflammation or irritation. They may also retard the absorption of topical anesthetics and prolong pain relief. If a bacterial throat or mouth infection requires an antimicrobial agent, one with specific toxicity that acts systemically, such as an antibiotic, should be used.

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6. *Recommended dose for oral health care products.* The Panel has defined and outlined below the general components of a dosage schedule for all products used in the oral cavity. The basis of the Panel's conclusions and recommendations are discussed in the general comments of each pharmacologic class and in the individual ingredient statements elsewhere in this document.

a. *Dosage range.* The Panel has examined the data submitted and concludes that, for purposes of clarity and accuracy, it is necessary to define the components of a dosage regimen. The components of a regimen for a particular product include a minimum effective dose, a usual single dose, a usual effective dose range, a maximum allowable single dose, and a maximum daily (24 hours) dose. These components of a dosage schedule are defined by the Panel in relation to a general OTC target population for which relief of symptoms is sought, such as minor pain due to sore throat, sore mouth, throat irritations, and antimicrobial activity.

(1) *Minimum effective dose.* The minimum effective dose is the amount of drug necessary to achieve the intended effect in some individuals in a significant OTC target population.

(2) *Usual effective dose.* The usual single dose is the amount of drug necessary to achieve the intended effect in most individuals in a significant OTC target population.

(3) *Usual effective dosage range.* The usual effective dosage range is the range between the minimum effective dosage and the maximum allowable single dose.

(4) *Maximum allowable safe dose.* The Panel finds that there may be circumstances when more than the usual single dose may be needed to provide an adequate effect. An increase in the usual single dose may be justified, for example, in individuals who, because of their age, body size or weight, or other factors, require a higher dose. The Panel defines the maximum single dose for most products as the maximum amount of drug that is safe and effective for use every 2 hours.

(5) *Maximum daily dose.* The maximum daily dose is the maximum amount of a drug that is safe and effective for use in a 24-hour period. Drugs that are sprayed or used as rinses or gargles may be absorbed through the mucous membranes or swallowed and absorbed from the gastrointestinal tract and thus produce systemic effects.

The Panel considers the adherence to a maximum daily dose necessary in the interest of safety. The clinical evaluation of some drugs clearly demonstrates side effects in the various organ systems and unwanted and sometimes dangerous symptoms. The maximum daily doses are indicated in the appropriate ingredient sections together with the adverse effects that can occur if these doses are exceeded.

*C. Determination of Safety and Effectiveness*

1. *Safety and effectiveness of ingredients for use in the oral cavity.* The Panel arrived at its conclusions and recommendations regarding the safety and effectiveness of all active ingredients after considering all pertinent data and information submitted. The Panel has adopted the following general guidelines:

a. *Safety.* The Panel's determination of the safety of single ingredients and combination products was based on the following criteria:

(1) The incidence and risk of adverse reactions and significant side effects when the agent was used according to adequate directions and instructions on the labeling.

(2) The potential for harm that might result from abuse or misuse under conditions of widespread OTC availability.

(3) Assessment of the benefit-to-risk ratio.

Ingredients and combination products that have been classed as Category I by the Panel require no further testing or evaluation for effectiveness or safety. Ingredients and combinations that have been classed as Category III for safety shall be subjected to testing outlined in the appropriate Data Required for Evaluation sections on Category III testing procedures. The manufacturer will be required to supply only the information that is missing and not all the information outlined in the section on testing.

b. *Effectiveness.* The Panel's determination of the therapeutic effectiveness of ingredients and combinations for use in the oral cavity was based on published and unpublished studies containing pharmacologic data considered by the Panel to be scientifically valid and pertinent. Clinical criteria for proof of effectiveness of a single agent or combination were determined by evaluating data from valid controlled studies, both subjective and objective, and by calling on the clinical expertise of the Panel members. These criteria will be discussed elsewhere in this document. (See paragraph C. of parts III., IV., V., VI., VII., and VIII. below—Data Required for Evaluation.)

Criteria for proof of effectiveness of the pharmacologic types of drugs evaluated were obtained from clinical studies which showed that an agent or combination caused a significant amelioration of the symptoms or provided a therapeutic effect for the stated indication in the labeling.

Ingredients or combinations that have been classed as Category III for effectiveness by the Panel shall be subjected to such testing as is required in the section on Category III testing procedures. Only that data which the Panel questions need be submitted unless the Panel concludes that the entire series of tests for effectiveness should be performed.

The majority of products used in the mouth and throat submitted to the Panel for review consists of combinations of active ingredients used together with pharmaceutical necessities listed as inactive ingredients. The remainder are single-entity active ingredients used with pharmaceutical necessities. The Panel recognizes that in order to be effective, the final product must be formulated properly and must conform to accepted pharmaceutical manufacturing standards. If not properly formulated, ingredients may not be bioavailable, or if they are bioavilable, they are present in less than the minmum effective dose or not in the form that exerts the intended therapeutic effects.

Important factors which the Panel considered in making its evaluations included the concentration of the active ingredients in the medium in which they are incorporated, the viscosity, the

volatility of the medium, the method by which the active ingredient maintains contact with the mucous membranes for the necessary length of time to assure a maximum therapeutic effect, the acidity or alkalinity of the medium, and the stability of the final product. Another important consideration to which the Panel gave weight was whether or not inert ingredients or active ingredients in a preparation interact or nullify the action of the principal active ingredients (Ref. 1). The designation of a pharmaceutical necessity as inactive or inert does not necessarily indicate that such an ingredient is chemically or pharmacologically inactive. An ingredient in a formulation containing more than one active ingredient could diminish the effectiveness of another ingredient by retarding its absorption in the mucous membranes or its passage into the lesion to which it is applied by altering the alkalinity or acidity of the medium and thereby changing the degree of ionization and its ability to penetrate epithelial barriers. The Panel also considered the effects of protein binding. Such binding could occur in such a manner that an ingredient would not be released to exert its claimed therapeutic effect or be absorbed (Refs. 1, 2, and 3).

The medium in which an active ingredient is incorporated not only must provide the necessary solubility and stability but also must maintain contact of the active ingredient with the surface upon which it acts.

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2. *Testing for recategorization of Category III ingredients.* When an ingredient or combination of ingredients is classfied as Category III because of insufficient data concerning its safety, effectiveness, or both, the manufacturer that produces such an ingredient or combination of ingredients must supply data to permit its reconsideration and reclassification from Category III to Category I. If such data are not available, the ingredient must undergo additional testing. The data submitted for reclassification should be available in the time period specified at the end of the description of each pharmacologic group. The Panel has indicated at the end of each section for each pharmacologic group protocols for obtaining data that are applicable to that particular pharmacologic group. General principles of the testing for reclassification applicable to all pharmacologic groups are outlined below.

The Panel considers the recommended protocols to be in agreement with the present state of the sciences of pharmacology and toxicology. The protocols suggested do not preclude the use of other newer, more refined laboratory or clinical investigative methods to establish safety or effectiveness of an ingredient. Manufacturers are expected to furnish only data relevant to unanswered questions in the ingredient sections or other sections of this document regarding the safety and effectiveness of the ingredients in their product. They are not expected to furnish all the data listed in the guidelines below.

Safety studies are required if the data submitted do not substantiate claims that an ingredient is safe when used as indicated in the labeling adopted by the Panel. Effectiveness studies likewise are required if the data submitted do not substantiate the claim that an ingredient or product is effective when used as indicated in the labeling adopted by the Panel.

a. *General considerations.* The Panel has categorized the ingredients it has evaluated in the following pharmacologic groups: (1) Anesthetics, (2) antimicrobial agents, (3) astringents, (4) debriding agents, (5) decongestants, (6) demulcents, and (7) expectorants. The ingredients of each category are grouped together, preceded by general descriptive introductory statements and followed by individual ingredient statements, labeling statements for the pharmacologic group, and data required for evaluation statements.

Certain general comments applicable to the preparation of protocols for the evaluation of all oral health care ingredients considered by the Panel are discussed below. Comments that are applicable only to a particular pharmacologic class and not to all OTC oral health care ingredients are considered at the end of the discussion pertaining to that particular pharmacologic group.

It is the consensus of the Panel that it is reasonable to allow 2 years for the development and review of evidence that will permit final classification of the safety and effectiveness of a Category III oral health care ingredient. The ingredients reviewed by the Panel and classified as Category III pose no serious problem or hazard for the consumer. Marketing need not cease during the time the product is undergoing testing. The Panel expects testing or reformulation to commece promptly. If data regarding adequate effectiveness and safety are not submitted within 2 years, the ingredients or a combination should no longer be marketed as an OTC product.

b. *Procedure for conducting studies on normal volunteer subjects and patients.* Investigational studies of a proper design should be conducted on human volunteers if reproduction of a particular lesion or oral cavity condition manifesting symptoms that are relieved as alleged in the labeling for indications is feasible (Ref. 1). Examples of experimental designs that may be appropriate and acceptable to the Panel include cross-over, double-blind, factorial, sequential trial, single-blind trial, and therapeutic equivalency studies (Refs. 2 and 3). Preference should be given to using double-blind studies with controls, so that the studies will demonstrate the effectiveness of the product. The cross-over technique should be used if possible. When used in a single-dose study, a period of 12 hours or more should elapse to allow elimination of an absorbed drug from the system. If repeated doses are used, longer periods of time should be allowed for such elimination. When the identity of an ingredient cannot be masked in performing a double-blind study and a suitable placebo is not available, control and treatment periods should be alternated if feasible. The control and treatment periods should be of sufficient duration to allow subjects to serve as their own control (Ref. 4).

A sufficient number of subjects should be use in such a study to permit statistical analysis of the data obtained (Ref. 1). The number of subjects tested should be sufficient to eliminated examiner bias, bias introduced by the placebo effect, and the effects of psychological responses to pain or to the symptoms in tested subjects. The subjects should be of both sexes and within the age groups for which use of the product is intended. The subjects should be healthy and free any ailment and should not be receiving any oral, parenteral, or topical medication. Female subjects should not be pregnant of menstruating (Ref. 4).

The study should be of sufficient duration to demonstrate effectiveness. The treatments should be performed on a random basis. The number and frequency of the applications of the preparation should be the same as

would be the case if the preparation were being used clinically. Any manifestation of local or systemic irritancy, sensitivity, or toxicity in these tests should be recorded and treatment discontinued.

When studies are performed in clinical situations, a large number of appropriate subjects with different types of oral cavity lesions or conditions presenting symptoms amenable to treatment by OTC oral health care products should be studied. Differentiation of patients should be made in accordance with the type and cause of a symptom. The randomization procedure should be used so that variables not otherwise controlled balance out (Ref. 5).

There should be detailed explanation of the criteria for assessment of the condition to be treated by the ingredient, of the method employed in testing, and of the validity of the method or methods used. Baseline demographic, medical, historical, and physical data for each subject should be obtained and recorded. Such data should include a medical history, a physical examination, laboratory studies, and other pertinent data (Ref. 6).

Studies should be performed on patients who have painful lesions, infections, or other afflictions in the mouth or throat that are amenable to treatment with OTC products. Subjects who have similar conditions and are being treated with a preparation should be divided into a treated group and a placebo group to obtain a controlled study (Ref. 7). Again, before-treatment data should be obtained and recorded. The degree of relief of symptoms, the onset of action, whether partial or complete, the duration of action, and the presence or absence of any rebound effect after the initial effect of the drugs wears off should be noted. A grading or scoring technique should be used to determine the degree of relief obtained from the symptoms being treated. The application of the product should be in accordance with the method outlined in the indication for use on the labeling. Tests should be performed using the final product formulation (Refs. 2 and 8).

The range between the minimum effective concentration and the maximal allowable (safe) concentration should be determined when lacking. This may be expressed in terms of the percent concentration of the preparation. Consideration should be given as to how the drug is absorbed or penetrates the mucous membranes, its duration of action, and its relationship to the length of time it remains in contact with a mucous membrane. Only the topical effect should be considered. The fact that a drug is absorbed and is detectable in the blood or is excreted into the urine in its pure form or as metabolites will not be accepted as evidence of effectiveness.

If not known, an attempt should be made to determine the possible mechanism of action or actions of the drug or drugs.

c. *Interpretation of data.* Detailed records should be kept. These should include legends, with specific explanation of codes, doses, mode, date, and time of application, the period of latency from the moment of application to the development of the desired therapeutic effect, the duration of the effect, the frequency of testing, and the duration of the test period. Investigative methods should be described in sufficient detail so that the experiments may be repeated by another investigator to verify and confirm results obtained from a particular investigator (Refs. 1, 2, 8, and 9).

Steps should be taken to eliminate examiner bias in both volunteer or clinical trials. Proper interpretation and explanation of the results should be provided. Whenever possible, statistical analysis should be employed to evaluate the results.

Positive evidence of drug effectiveness should be obtained from a minimum of two studies based on the results of two different investigators or laboratories.

All data submitted to FDA must present both favorable and unfavorable results.

d. *Safety evaluation.* Adequate, acceptable, controlled in vivo studies of acute and chronic toxicity in several species of animals should be supplied. The oral $LD_{50}$ (mean lethal dose) in animals should be established and, if possible, the range of the toxic dose in man should be made available. This is important particularly since individuals, especially children, may accidently ingest an overdose or inhale excessive quantities of these medications (Refs. 1 and 10). Chronic toxicity studies of ingredients classified as Category III should be performed by two independent investigators (Refs. 11 and 12).

Tests for irritancy should be performed. These should include acute eye irritation, primary skin irritation, corrosivity, acute and subacute dermal toxicity, and sensitivity in animals (rabbits). Tests for topical irritancy on the oral and pharyngeal mucous membranes, including sensitization of the skin, and systemic sensitivity in man, should be performed if feasible. Methods for testing for irritancy and sensitivity are described below.

Data on systemic absorption, distribution, the metabolic fate, the rate of excretion, and possible cumulative effects should be supplied as discussed in the ingredient statements of this document.

e. *Recommended toxicological studies.* A variety of toxicological data can be obtained to demonstrate that a preparation is safe. Manufacturers are expected to conduct the applicable studies listed below. The Panel emphasizes that this requirement does not preclude the use of better testing methods which may be developed in the future. The Panel recommends that the following data be obtained in animals for the active ingredient(s) and for the formulation(s) intended for use on the mucous membranes of the mouth and throat.

(1) *Preclinical animal studies.* (a) Acute oral $LD_{50}$ toxicity in rats.

(b) Acute eye irritation in rabbits.

(c) Primary skin irritation and corrosivity in rabbits or other suitable animals.

(d) Acute toxicity on the oral and pharyngeal mucous membranes in rabbits or other suitable animals (Refs. 11, 13, and 14).

(e) Acute toxicity of inhaled aerosols and sprays in rats or other suitable animals.

(f) Skin sensitization studies in rabbits and guinea pigs or other suitable animals.

(2) *Irritancy and sensitivity studies in humans.* A number of methods embodying the use of patch testing have been proven of value in determining skin irritancy and systemic sensitization. The Panel recommends that one of the following methods of patch testing be performed:

(a) The Draize human skin irritancy and sensitization tests or one of the various modifications may be used. The testing should be performed on the skin of the subject's back or arm (Refs. 1 and 15).

(b) The method of Shelanski and Shelanski (Ref. 16), in which the active ingredients or the formulation under study is applied at frequent intervals of 1 or 2 days to the test site for 3 to 4 weeks may be used. After a rest period of 2 weeks, a single dose of the drug or formulation is applied as a challenge (Ref. 16). The preliminary applications are made to detect primary skin irritants and provoke sensitization in susceptible individuals. The challenging dose detects whether or not the drug is a skin sensitizer.

(c) The maximization procedure of Kligman (Ref. 17) or one of its modifications uses an irritant which is

applied over a desquamated test site. Desquamation is performed by using a rubbing technique which facilitates penetration, thereby hastening and accentuating the skin-sensitizing potential of a substance (Ref. 17).

Solvents and other substances that are classed as inert ingredients used to formulate a finished product are indeed active in many instances and may penetrate the mucous membranes of the mouth and throat or can be swallowed. These are absorbed and detoxified or excreted in the same manner as the active ingredients. It is possible for highly lipophilic substances used daily for long periods of time to accumulate in the adipose and other lipid-rich tissues, particularly if they are not readily biodegradable. They may remain in the tissues for days, weeks, or months and produce chronic toxicity (Refs. 8, 9, and 18). However, none of the ingredients the Panel has evaluated are retained for long periods of time in adipose or lipid-rich tissues. Animal studies should be performed as a preliminary to human in vitro testing (Ref. 1).

The Panel recognizes that the clinical studies and studies on volunteers in the case of many ingredients will be subjective since objective methods are not available in many cases. This is applicable particularly to studies of preparations that relieve pain and discomfort. The Panel accepts such studies if they are performed according to the guidelines outlined above. The Panel also recognizes that certain ingredients have a dual action. An expectorant may relieve discomfort or soreness in the throat by acting both as a debriding agent and a detergent. The Panel accepts data for evaluation applicable to the principal action a drug manifests when such overlapping of action exists.

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*D. Labeling of OTC Oral Health Care Products*

The Panel emphasizes the importance of specific informative and truthful labeling so that the consumer can select the most appropriate product for his/her condition and use it in the prescribed manner appropriate for obtaining the claimed therapeutic effect.

The Panel reviewed the general labeling requirements previously adopted by FDA for OTC products (21 CFR Part 201). These requirements provide for labeling information on the principal display panel of the packaging form, a statement of identity, the indications for use, the identity of ingredients, directions for use, other allowable information such as product performance or attributes, and general and specific warnings. The Panel concurs that these general requirements are appropriate for labeling of OTC preparations intended for use in the mouth and throat. The labeling of individual active ingredients will be discussed elsewhere in this document.

After reviewing all submitted labeling of OTC products used in the mouth and throat, the Panel recommends the following additional requirements:

1. *The statement of identity.* The statement of identity in the labeling of the product should contain the established name of the drug, if any, and should identify the product as an "oral health care product." It should also identify the pharmacologic class(es) of ingredient(s) contained within the product, i.e., antimicrobial, anesthetic, demulcent, astrigent, expectorant, debriding agent, or decongestant. When two or more active ingredients are combines and each is listed as an active ingredient, each ingredient shall be included in the statement of identity. The therapeutic action of a pharmarcologic class of an ingredient may not be used in the labeling indications described below because these terms do not denote the symptoms or disease process for which they are intended to be used.

2. *Ingredients.* The Panel concludes that products intended for use in the mouth and throat should contain only active ingredient(s) plus such inactive ingredients (pharmaceutical necessities) as are necessary for product formulation. All such drug products should also identify the active and inactive ingredients in the labeling by their established names. Terms such as "aromatics," "essential oils," and other vague connotations give no specific description of the identity of ingredients and should not be used. The Panel will,

however, accept terms that are specific and are actively descriptive, such as "oil of lemon," "oil of cloves," etc. Since the United States is slowly converting to the metric system, the Panel recommends that metric units be used in labeling.

The Panel concludes that the exact quantity of all active ingredients should be stated on the label in percent by weight or volume, in metric equivalents, and in the amount present in a unit dose by weight if the ingredient is a solid. If the active ingredient is a liquid, delivered in a unit dose, the amounts should be stated by weight or volume.

The Panel strongly recommends that the inactive ingredients also be listed on the label. "Inactive ingredients" are not necessarily inert and inactive and may cause drug interactions if ingested with other medications or cause toxic manifestations in cases of overdosage of the product. The Panel excludes from this requirement flavorants or coloring agents which are present in insignificant quantities.

The Panel believes that consumers are entitled to full disclosure of products used for self-medication and that each inactive ingredient should be stated on the label. The purpose each inactive ingredient serves in the formulation, such as for coloring, as a flavorant, or solvent, preservative, or vehicle, should also be stated in the labeling. These data are essential when poisonings are suspected, reactions due to hypersensitivity arise, or irritations develop. A minority of the Panel believes the quantity of the inactive ingreients should also be listed on the label.

The Panel concludes that therapeutic ingredients that are pharmacologically or chemically active in therapeutic concentrations can be designated by the term "inactive ingredients" only when they are necessary for proper formulation and are present in less than therapeutic concentrations.

It is the consensus of the Panel that the term "inert ingredients" be restricted to those ingredients that are chemically inert or insoluble in vivo and not absorbed by living cells. Examples are calcium sulfate, silica gel, and activated charcoal.

3. *Indications and directions for use* The indications for use of oral health care products should be simply and clearly stated, should provide the user with enough information for effective and safe use of the product, and should include the statement that the product is for the temporary relief of symptoms. No reference should be made or implied regarding the alleviation or relief of symptoms unrelated to a condition that is not an indication of the product.

The Panel recognizes that indication statements for oral health care products could be worded in a variety of ways and convey the same meaning, but for the sake of simplicity, clarity, and in the interest of minimizing consumer confusion the Panel recommends a restriction of indications for oral health care products. In addition, the Panel believes that limiting indications would protect the consumer from unfounded, misleading, and possibly hazardous claims. It would also eliminate similar products having different indications. The Panel concludes that the consumer would greatly benefit from such labeling.

The directions for use of oral health care products should be clear and provide the user with a reasonable expection of the results the product produces. The directions should be as detailed as possible and placed conspicuously on the label. The Panel would like to emphasize that the quantity of a product that is used, its mode and frequency of application, and its duration of contact with or over the area in which the symptom is located are all important considerations and have a definite bearing on the effectiveness of a product. Therefore, the Panel recommends that careful consideration be given to development of directions for use for oral health care products.

a. *Category I indications*—(1) *For anesthestics/analgesics.* "For the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat."

(2) *For astringents.* "Aids in the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat."

(3) *For debriding agents.* "Aids in the removal of phlegm, mucus, or other secretions in the temporary relief of discomfort due to occasional sore throat and sore mouth."

(4) *For demulcents.* "Aids in the temporary relief of minor discomfort and protects irritated areas in sore mouth and sore throat."

b. *Category II indications.* Labeling for OTC oral health care products should be symption oriented and not disease oriented. Labeling statements should not suggest or imply a cure or amelioration of a disease process or list a disease entity for which a product is not effective. The Panel believes that consumers with specific diseases or pathologic lesions should be under the care of a physican and that labeling referring to diseases that require medical intervention may mislead the consumer. Labeling of this type could encourage self-diagnosis or self-treatment of conditions not amenable to OTC therapy. Self-medication may lead to the progression of a disease process particularly if taken in inadequate doses or intermittently for pain relief or other conditions over prolonged periods of time by individuals who have persistent symptoms. In addition, any reference to pharyngitis, glossitis, tonsillitis, gingivitis, aphthous ulcers, or Vincent's infection in OTC oral health care product labeling is unacceptable to the Panel.

The Panel concludes that claims that state or imply that the prophylatic use of an OTC oral health care product maintains a healthy state in the mouth or throat are misleading to the consumer. Therefore, the Panel recommends that any medicinal claims for "prevention" not be allowed.

The Panel recommends that indications not recognized by the medical community be placed in Category II. For example, the Panel does not know what is meant by such indications as "irritable throat," "soothing lubricant," and "relieves stomatitis" and believes that consumers would also have trouble comprehending them.

The therapeutic or pharmacologic class of an ingredient, such as expectorant, anesthetic, or astringent, should not be used in the labeling indications because they do not denote the symptoms for which they are intended to be used. Cosmetic claims are not acceptable as indications for OTC oral health care products.

The Panel has placed in Category II those indications that are not supported by scientific data or sound theoretical reasoning or are inaccurate, misleading, or make claims that exceed those allowed for OTC products. The indications that the Panel recommends be in Category II are listed in the Category II labeling sections of each individual pharmacological group of ingredients.

c. *Category III indications*—(1) *For antimicrobials.* "For the temporary relief of minor sore mouth and sore throat by decreasing the germs in the mouth."

(2) *For decongestants.* "Aids in the temporary relief of occasional discomfort due to congestion in the mouth and throat."

(3) *For expectorants.* "Aids in the removal of secretions and in the temporary relief of discomfort due to occasional sore throat and sore mouth."

(d) *Claims deferred to other Panels.* Certain labeling claims have been deferred to other panels or to FDA for review since these claims involve anatomic areas other than those defined

as the boundaries of the Oral Cavity Panel; therefore, the claims are not within the scope of this Panel. The following claims have been deferred to the appropriate panels for consideration:

"Gum massage," "Prevents infection in burns, abrasions, minor cuts, open wounds, scalds, skin irritations, and sunburn," "For soreness or discomfort caused by denture irritation following tooth extraction or other minor gum irritation," "Temporary relief of pain and discomfort following periodontal procedures and minor surgery of the mouth," "For management of body odor or repair of gum tissues," "Relief of discomfort, deodorization, and minor gum disorders," "Before and after gingivectomy or curettement," "After extractions and under immediate dentures," "To promote healing and to relieve itching and discomfort and deodorization in minor wounds," "Burns, surface ulcers, cuts, abrasions, and dentures," "Indigestion relief," "For fast temporary relief of nasal congestion," "Fast temporary relief of nasal congestion and minor throat irritation," "Relief of postnasal drip, gum irritation, and sinusitis," "Promotes needed expectoration," "For fast temporary pain relief of minor denture irritation, toothache, teething, and cold sores," "Fast pain-relieving antiseptic for sores, cuts, burns, insect bites, fever blisters, and cold sores," "Relieves irritated gums, athlete's foot, poison ivy, poison oak, and itchy bites from chiggers, mosquitoes, and flies," "Relieves pain from minor injury, such as minor cuts, burns, scratches, abrasions, razor nicks, chafed or irritated skin, and painful sunburn," "Helps to prevent the spread and reinfection of acne," "Breathe easier when nose is clogged due to cold, hay fever, sinusitis," "Pain-relieving antiseptic for athlete's foot," "Dry dressings," "Prickly heat," "Refreshing for hot, tired, perspiring feet," "For dry dressings and prickly heat," "Combats infections, soothes pain, and promotes rapid healing," "For superficial wounds, cuts, minor burns, cold sores, fever blisters, poison ivy, sunburn, and chafed skin," "Soothes, cools hot irritated skin of prickly heat."

4. *Warnings.* The Panel recommends that additional statements be included in the labeling of oral health care products for proper use and adequate consumer protection. These statements are listed under the general headings of warning statements.

The Panel agrees with the current regulation (21 CFR 330.1(g)) containing the general warning statements, "Keep this and all drugs out of the reach of children" and "In case of accidental overdose, seek professional assistance or contact a posion control center immediately." The Panel considers these to be reasonable and proper statements for all OTC medications. Specific warnings or precautions that alert potential users of possible serious side effects of therapeutic doses, drug interactions, and especially the sequence of reactions due to overdose or drug interactions will be described in the discussion of each pharmacologic class or in individual ingredient statements elsewhere in this document.

The Panel also concurs with the recommended warning in the regulations (21 CFR 369.20) pertaining to throat preparations for the temporary relief of minor sore throat which states: "Warning—Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by physician."

Because OTC products may be purchased by anyone, the Panel is concerned that the public generally does not regard OTC products as medicines which, if used improperly, might result in injurious or potentially serious consequences. The public must be made aware of the concept that these products, like all medicines, carry some risk and should be used only as directed for the temporary relief of symptoms and not indiscriminately. The Panel, therefore, concurs with the FDA and considers it prudent to include the general warning statements now required by § 330.1(g) (21 CFR 330.1(g)).

The consumer should be informed of any possible signs of known toxicity, adverse reactions, or any warning requiring discontinuation of the use of the drug so that appropriate steps may be taken before more severe symptoms become apparent or the condition worsens. For example, one of the first symptoms of iodism due to overuse of iodine-containing compounds is stuffiness of the nose. (See Part IV. B.3.n. (1) below—Safety.)

Specific warnings that pertain to an ingredient appear below and in the discussions of individual ingredients. The consumer should also be warned of possible drug interactions that might occur when a product is taken concomitantly with other OTC products or medications prescribed by physicians. Such labeling should be conspicuously placed so that it will not be overlooked by the consumer.

The following are general and specific warning statements recommended by the Panel for use in the labeling of OTC oral health care products:

a. *Statements for use in the labeling of all OTC oral health care products.* (1) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(2) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

b. *Statements for use in the labeling of OTC oral health care products as specified*—(1) *For products containing phenylephrine hydrochloride or phenylpropanolamine hydrochloride.* (i) "Do not use this product if you have thyroid disease, high blood pressure, diabetes, or heart disease except under the advice and supervision of a physician."

(ii) "Do not use if taking monoamine oxidase inhibitors. Discontinue use if dizziness, headache, fast pulse, tremors, or nervousness develop. Consult a physician if symptoms persist."

(2) *For products containing aspirin.* (i) "Do not use if you are sensitive or allergic to aspirin."

(ii) "Do not use if you have a bleeding problem or if you are on anticoagulants."

(iii) "Do not use without a physician's or dentist's advice if your mouth is highly irritated or ulcerated."

(iv) "Do not use after surgery in the mouth or throat."

(v) "Provide good fluid intake when aspirin or aspirin-containing preparations are used."

(3) *For products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

(4) *For products containing glycerin.* "Do not use full strength. Dilute with two or three volumes of water."

5. *Labeling of product attributes.* The Panel accepts the use of terms that describe certain physical and chemical qualities of OTC oral health care products that are indicative of product performance so long as none of these terms implies that it is an indication that the product exerts a therapeutic effect, e.g., "pain reliever," "astringent," "demulcent," etc. The attributes described must pertain to product performance or to the pharmaceutical attributes of the formulation. The properties described may be due to the effects of colors, taste, or smell of specific inert or inactive ingredients

included in the final product formation. Such product characteristics in the labeling must be placed apart from the "indications" but must be in a conspicuous part of the labeling so that the consumer will be fully aware of their existence. Such labeling may be intended to make the product more appealing to the consumer. The Panel stresses that the terms used in such labeling must be carefully selected so that they do not imply that they exert any therapeutic effect or relieve any symptom, temporarily or permanently, or that they ameliorate a disease process or exert a curative effect.

The use of medicinal odors has been associated with the practice of medicine and pharmacy since the art of therapeutics was first conceived. This is of particular importance in oral health care products since smell and taste are closely associated. Although many chemical and instrumental methods have been used to measure quantities of substances emanating from the body that cause specific ordors, the cosmetic and pharmaceutical industries often rely on the personal reactions of trained individuals using subjective methods in making such assessments and measurements.

More important than color and odor is the matter of the taste of a product, particularly one intended for OTC use. The listing of flavorants and essences that are used for disguising odors and the fact that flavors of certain medicines are in official compendia attest to the acceptability of the practice by the community, the pharmaceutical industry, and the consumer of using these agents. Flavors that sweeten a final product containing a bitter ingredient are especially important. Description of the flavor in the labeling is particularly important when a product is formulated with several different flavors (i.e., cherry v. orange v. lemon) because one flavor may appeal to one consumer and not to another.

The Panel concludes that the practice of using descriptive labeling is both reasonable and informative to the consumer and not objectionable because it actively reflects inherent characteristics and the performance of the marketed product. Terms such as "does not stain," "pleasant tasting," and "non-oily" are acceptable. The Panel finds any claims related to product performance that cannot be substantiated by scientific data unacceptable. Labeling containing phrases such as "acts fast," "gives quick relief," "long-acting," "remarkable," or "acts promptly" is misleading and may be confusing to the consumer and is not permitted unless such claims can be supported by adequate scientific data.

*E. Adverse Reactions*

Most ingredients used in oral health care preparations are absorbed from the mucous membranes of the mouth or throat and pass systemically into the blood stream. They may be swallowed deliberately, as is the case when lozenges are sucked slowly over a period of time, and pass into the gastrointestinal tract, where they are absorbed and circulate systemically. In many cases absorpotion from the mucous membranes of the mouth and throat is more rapid than from the gastrointestinal tract. Ingredients may be absorbed in sufficient quantities during even a brief rinse or during gargling to produce systemic effects (Refs. 1, 2, and 3).

Certain oral health care ingredients produce unwanted or adverse effects regardless of how they are administered. Adverse effects to drugs are generally categorized as acute overdosage, chronic overdosage, secondary effects, intolerance, idiosyncrasy, local irritancy, local hypersensitivity, and systemic hypersensitivity (allergic) reactions. Side effects are not adverse reactions but are sometimes erroneously classed as such. Adverse reactions may be local or systemic or a combination of both (Ref. 4).

1. *Overdosage.* Overdosage, often referred to as acute toxicity, may occur after taking a single dose that is in excess of the therapeutic dose, by accumulation after repeating therapeutic doses at frequent intervals, or by deliberate ingestion of massive doses. Overdosage is usually manifested as an exaggerated form of the pharmacologic action or actions typical of the drug. However, ingestion of massive quantities may produce symptoms in addition to the exaggeration of the pharmacologic action typical of the drugs. The acute manifestations and residual effects of overdosage vary with each drug. The symptoms and severity are often dose-related (Refs. 4 and 5).

Gross overdosage may result in toxic and, in some cases, fatal reactions. Ingestion of massive quantities of some drugs may produce coma, cause convulsions, paraplegia, respiratory failure, hemorrhagic states, and other effects not ordinarily characteristic of the drug (Refs. 4 and 5). Phenol, in toxic doses, may cause convulsions and respiratory failure. The manifestations of overdosage of oral health care products are described in the ingredient statements under the sections on safety.

2. *Chronic overdosage.* Chronic toxicity may result from prolonged usage of the usual recommended doses or by repeatedly using subtoxic doses. Such usage may result in cumulative effects of the drug or its metabolites in the tissues and, in most cases, will present manifestations different from acute overdosage. Chronic exposure to or prolonged usage of a drug that ordinarily causes no ill-effects after several usages may produce irreversible changes in some organs. Antiseptics containing organic mercury permanently damage the kidneys. Chronic usage of phenolic compounds may result in cellular changes, discoloration of the skin, etc. (Refs. 4 and 6).

Chronic, long-term usage or overusage and its resultant manifestations are extremely important when considering OTC oral health care preparations, particularly gargles, rinses, or sprays, containing active ingredients such as quaternary nitrogenous compounds, iodophors, and phenolic compounds which are used on a day-to-day basis for weeks, months, or years at a time (Refs. 7 and 8).

Manifestations of chronic toxicity may often be delayed. This is sometimes referred to as remote toxicity. The remote toxicity of many of the newly added drugs, such as the "quats," is not known.

3. *Side effects.* The term "side effects" refers to one or more therapeutic effects that a drug may possess in addition to the principal therapeutic effect. Few drugs have a single pharmacologic action and considerable overlapping of actions is found among drugs. For example, the "caine" type of local anesthetics, such as procaine, manifests some antihistaminic and anticholinergic activities. These side effects are not harmful, but are often unwanted. The dryness of the mouth and visual disturbances caused by anticholinergic drugs, the drowsiness caused by antihistamines, and the pressor effects caused by vasoactive adrenergic drugs used as decongestants are examples of side effects that may not be harmful but are unwanted in some instances and desirable in others (Ref. 4).

The term "side effect" actually has no specific pharmacologic connotation and is not synonymous with the term "adverse reaction." It is sometimes used deceptively to convey the impression that an adverse effect is not necessarily undesirable, unpleasant, or harmful. Dryness of the mouth is desired and sought when an anticholinergic drug is administered to prevent formation of an excessive secretion of saliva, but unwanted when an anticholinergic drug is used as an antispasmodic or bronchodilator.

A true adverse effect of a drug differs from a side effect in that the adverse effect has no therapeutic usefulness, is undesirable, and may even cause harm. Nausea caused by gastric irritation following the use of an oral antibiotic would be an example of a true adverse effect. It is neither wanted nor is it therapeutically useful (Ref. 4).

4. *Secondary effects.* Secondary effects are indirect effects that occur during or after the use of a drug and do not result from any direct action of the drug itself on a particular organ system. An example would be the use of certain antimicrobial agents in the oral cavity that alter the normal bacterial flora and cause an overgrowth of symptom-producing pathogenic bacteria, or fungi, such as candida. The antimicrobial agent itself plays no direct role in accelerating the growth of such organisms but alters the environment and favors their growth (Refs. 4 and 6).

5. *Intolerance.* "Intolerance" is a term that describes a lower-than-the-average threshold to an anticipated response to a drug. The response is one normally expected of a drug, but the dose required to elicit that response is much less than is necessary to affect a significant group of a target population. Thus, a preparation containing an ingredient in a dosage form that ordinarily produces the usually anticipated response in a target population would cause an exaggerated response in a susceptible person exposed to the usual effective dose. Since many ingredients used in oral health care products are readily absorbed through the mucous membranes, intolerance may be encountered, although this is uncommon. For example, 10 milligrams (mg) of phenylephrine in a lozenge causes no pronounced pressor effect. In an intolerant individual it could produce a pronounced hypertensive response. Tolerance to a drug is often dependent upon a patient's physical condition (Ref. 5).

6. *Idiosyncrasy.* "Idiosyncrasy" is a term used to denote a qualitatively abnormal and unanticipated reaction produced by a drug in a particular, isolated individual in a target population. The reaction is not one ordinarily anticipated from use of the drug and is not one for which the drug is used therapeutically. A decongestant causing hypotension, instead of a pressor effect, or an analgesic causing hyperanalgesia or antianalgesia (exaggeration of a pain) would be examples of idiosyncrasy or idiosyncratic reactions (Refs. 4 and 9).

The term is often used erroneously to indicate that a reaction is due to hypersensitivity or an allergic state. The mechanisms involved in producing an idiosyncratic reaction and an allergic response are distinct and separate. The distinction is discussed in detail below. Ingredients used in oral health care products occasionally cause idiosyncrasy, but such reactions are uncommon. Aspirin in gum may cause an asthamtic attack in a nonallergic individual which could be ascribed to idiosyncrasy. The response is not immunogenic but is due to some interference with prostaglandin synthesis. In others who are truly allergic, the response is immunogenic in origin. The reaction would then be classed as sensitivity. Aspirin can cause both types of adverse reactions.

7. *Local irritancy.* Some ingredients in oral health care products possess the propensity for producing local reactions. Among these reactions are "irritation" of the mucous membranes (Ref. 10). Ulceration in the mouth or throat may appear after one or more applications of an ingredient when none existed prior to its use. This type of response is due to a direct irritating effect of an ingredient on the mucosal and submucosal cells. Caustic agents, such as phenol, cresol, and certain astringents, may have locally irritating effects. Locally applied aspirin tablets or aspirin-containing gums have produced aspirin burns. In some cases, the irritating response may appear early, sometimes immediately after application of a preparation. In other cases, it may be delayed and appear after one or several applications. No immunological phenomena are involved in this type of direct irritancy. The susceptibility to this type of response is difficult to detect beforehand. Patch and other tests on the skin employed by dermatologists and allergists may give no clue that this type of reaction will occur (Refs. 6 and 11).

8. *Local sensitivity.* In addition to "irritancy," ingredients in oral health care products produce a type of sensitization involving immunological phenomena. The manifestations of such sensitization may be local or systemic. Topical sensitization may result from prolonged or repeated contact of an ingredient with the mucous membranes of the mouth and throat (Refs. 12 and 13). Under these circumstances, an ingredient may serve as a contact allergen by acting as a hapten becoming bound to the protein in the cells of the mucous membranes or submucosal structures. Stimulation of the T cell division of the lymphoid system occurs. Lymphoid cells become sensitive to the contact allergen or the hapten and accumulate in the mucosa, the submucosal layers, or even in the skin. The drug may pass through the mucous membranes, circulate in the blood, combine with proteins in the skin, and not sensitize the mucous membranes. Contact of the sensitized lymphocytes with the ingredient at a later date provokes a cell-mediated sensitivity type of reaction characterized by inflammation, burning, erythematous ulcerations, or exudation at the site of application. This type of response is cytotoxic, since it affects lymphocytes and no immune bodies are involved (Refs. 13 and 14). Topical sensitization of this type may, at times, be difficult to distinguish from direct topical "irritancy." The resulting contact sensitivity in a particular individual manifests immunological specificity for the particular ingredient (hapten). Patch-testing may be helpful in detecting this type of sensitization when the skin has been sensitized. However, since the proteins of the skin differ from those of the mucous membranes and the hapten may not have passed into the skin a negative patch skin test may be misleading because sensitization may have occurred in the mouth and throat even though the skin has not become sensitized. Contact of the agent with the mucous membranes would produce a reaction. Coombs and Gell (Ref. 13) have classified immune responses into four distinct types. They designate this type of response as Type IV (cytotoxic). It has also been called "delayed hypersensitivity." The allergen or the hapten interacts with the sensitized lymphocytes in the mucous membranes, or submucosal tissues. The lymphocytes disintegrate and produce tissue damage (Ref. 15).

9. *Systemic sensitization.* A hapten may be inhaled, injected, taken orally, come in contact with a mucous membrane of the mouth or throat, trachea, lungs, and other organ sites, or pass through damaged skin and bind with proteins in blood and other tissue fluids to produce a systemic type of sensitization. This was once referred to as the "humoral type" or immediate type of sensitization. This type of sensitization is due to circulating IgE of the blood protein fraction. Coombs and Gell (Ref. 13) designate this type of response as the Type I response. It occurs in the allergic-prone (atopic) individual and is associated with a hereditary tendency towards sensitization. Allergens (also called antigens) are usually proteins or lipoproteins of high molecular weight. Drugs of low molecular weight, often referred to as haptens, combine with proteins and act as allergens that cause a systemic type of sensitization by

stimulating the production of circulating antibodies (immune bodies) of the IgE class of globulins (Refs. 16 and 17).

Antibodies are found in the globulin fraction of blood proteins. Ordinarily, immune bodies are protective and neutralize an antigen, allergen, or a hapten on contact by forming an antigen-antibody complex which is harmless to the organism and prevents a reaction. In susceptible individuals, for unknown reasons, the antibody acts in an adverse (pathologic) manner and sensitizes certain cells in the body, referred to as target cells. IgE antibodies have a cytophilic affinity for the membranes of mast cells, blood neutrophils, and basophils in susceptible individuals (Ref. 13). These antibody-sensitized cells rupture on subsequent contact with the appropriate allergen or hapten (drug) and release vasoactive substances that dilate or constrict blood vessels. At least one or more exposures and an incubation period of at least a week are necessary for immune bodies and this type of sensitization to develop. The B cell division of the lymphoid system is involved in the systemic type of immune response (Ref. 13). It is due to circulating antigens. The presence of antibodies that sensitize cells is necessary for sensitivity reactions to occur. This type of sensitization may be manifested by anaphylaxis, extrinsic asthma (systemic), rhinitis (systemic), subcutaneous edema, laryngeal and pharyngeal edema (systemic), urticaria, or atopic dermatitis (Refs. 14 and 16).

Antigens have certain groups of amino acid complexes on their structure which determine the specificity of the antigen and the type of antibody that forms. These chemical sites are called antigenic determinants. The antibody has certain receptor sites on its molecule into which the antigen determinant fits in a lock-and-key manner to form the antigen-antibody complex. Each antigen has its own number of natural groups of antigenic determinants. When a drug acts as a hapten, an additional antigenic determinant not ordinarily found on the antigen is added to the protein. In the production of the antibody, a receptor forms on the antibody that accepts the hapten-protein antigen or the hapten itself (Ref. 17).

Drugs that are in the same chemical family may produce cross-sensitization or may cross-react in susceptible individuals if the antigenic determinant or hapten can fit into the same receptor of an antibody. However, even a slight modification of the chemical structure between two closely chemically allied drugs may negate this type of reaction. Aminobenzoic acid, for example, is closely allied chemically to its ester, ethyl aminobenzoic acid (benzocaine). Yet, it does not necessarily follow that both of these compounds, even if they bind on the same antigenic determinant of a protein, will cause cross-sensitization unless they fit into the same receptors on the antibody (Ref. 13). The Panel finds that the incidence of cross-sensitization of drugs used in oral health care preparations is low and does not consider this to be a serious problem.

Human IgE antibodies will also bind to the plasma membranes of mast cells in the skin and mucous membranes and cause sensitivity reactions when the appropriate antigen (or hapten) circulates in the blood or comes into contact with these cells following oral ingestion, parenteral injection or percutaneous absorption. The response may be local or generalized and even may be cutaneous (Refs. 9, 16, and 17).

The systemic type of sensitization differs from the topical sensitization which is due to a contact allergen. A topical sensitization causes a cell-mediated type of reaction. A systemic type of sensitization elicits an adverse response to an antigen-antibody complex acting on sensitized target cells (Ref. 13). The anaphylactic type of reaction is the most serious. It may occur suddenly, with little or no warning, and may be fatal. A trace of the offending ingredient coming into contact with the mucous membranes or administered orally or parenterally to a sensitized person may precipitate the sudden release of mediators, such as massive quantities of histamine, serotonin, slow-reacting substance (SRS–A), the eosinophilic chemotaxic factor or various kinins. These mediators, acting on the blood vessels, cause them to dilate and may cause syncope, shock, and death in a matter of minutes. These substances are released from the mast cells and white blood cells, particularly basophils and neutrophils. Fortunately, this type of reaction is rare.

Marketing experience of oral health care products indicates that the frequency of anaphylaxis from topical application on the mucous membranes has been infrequent. A drug itself may act directly, in the absence of immune bodies, on mast and other cells and cause histamine or other mediator release. This type of reaction is often called anaphylactoid. It resembles anaphylaxis except that the causative mechanism is different (Ref. 13).

Fortunately, this type of reaction also is uncommon. Testing for sensitivity, particularly for anaphylaxis in allergic patients, may be dangerous because the quantity used for testing may be fatal in susceptible individuals. An anaphylactic or anaphylactoid reaction may occur the first time a drug is applied topically to a mucous membrane or to the skin. The anaphylactic and anaphylactoid types of reactions may be delayed, but the manifestations, when fully developed, are similar to the immediate-occurring type (Ref. 16 and 17).

Other manifestations of systemic sensitization that may occur are relatively benign and disappear with proper treatment or discontinuing use of the drug. Among these manifestations are rhinitis, asthmatic attack, urticaria (hives), and atopic dermatitis. Generally, histamine is the most common offender in causing these responses, but other mediators may also be responsible (Ref. 18).

All soluble drugs can act as haptens and cause sensitization. Antihistamines, despite the fact that they are used systemically for treating allergies, can act as haptens and be sensitizers when applied topically. The "caine" types of local anesthetics and modifications of the "caine" type cause sensitization to a greater extent than the alcohol type of ingredients although the alcohols may also produce irritancy and sensitization. The quaternary nitrogenous derivatives can also act as haptens and be sensitizers when applied topically. Similarly, phenolic-type compounds and pharmaceutical necessities such as flavorants can act as haptens (Refs. 16 and 19).

People who are allergic to foods, inhalants, and other substances are high risks and are more apt to become sensitized to drugs (Ref. 10).

Data are meager on the frequency of sensitization by ingredients used in oral health care products and on the relationship of occurrences in a target population. The Panel believes that the long-term usage and marketing experience, over many years, of the majority of these ingredients justifies their continued use and that the hazards due to sensitization are minimal. The labeling of oral health care products must indicate that a product should not be used if a subject is known to be sensitive to any of the ingredients used in its formulation. The Panel recommends the following general warning in the labeling of all active ingredients in oral health care products: "Discontinue use and consult a physician if irritation persists or increases or a rash appears on the skin."

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*F. Principles Applicable to Combination Products*

1. *General comments.* In reviewing OTC oral health care preparations for use on the mucous membranes of the mouth and throat, the Panel was mindful of the OTC review regulations (21 CFR 330.10(a)(4)(iv)) which state:

> An OTC drug may combine two or more safe and effective ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual acting ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concurs with the basic concepts embodied in this regulation that each active ingredient in a combination product must contribute to the claimed effects and that the combination must provide rational concurrent therapy. The Panel believes that it is irrational to use a combination product unless each active ingredient contributes to the effective treatment of at least one of the labeled symptoms for which the combination of ingredients is recommended.

The Panel has outlined below the proposed standards for combinations for all the ingredients reviewed. Also included are elaborations and reasons for the rationality or irrationality of combining the various ingredients with each other and other Category I ingredients considered by other panels.

It is accepted medical practice to use only drugs that are necessary to safely and effectively treat a patient. Only single-ingredient products are used to treat a particular symptom or disease entity in most cases. The Panel believes strongly that this concept should apply to self-medication as well since the consumer is treating symptoms without the advice of a physician. OTC products containing effective single active ingredients are, therefore, preferred to those having multiple active ingredients. Products containing a single active ingredient reduce the possibility of the occurrence of toxic, allergic, and idiosyncratic reactions, and possible unrecognized and undesirable drug ineractions. This is the case when a drug is prescribed by a physician and should also be the case when a drug is used by a layman for self-treatment. It is the opinion of the Panel that in general OTC oral health care preparations should contain only one Cateogry I active ingredient of a pharmacologic class and such inactive ingredients as are necessary for pharmaceutical formulation.

The Panel recognizes that select situations may exist in which combinations of ingredients from the same pharmacologic class of Category I active ingredients or from different pharmacologic classes but exerting similar therapeutic effects may be used to treat the same symptoms or conditions. The Panel does not wish to deprive the consumer of the right to use these products if they possess a therapeutic advantage not possessed by each of the individual ingredients used alone. By "therapeutic advantage" is meant that the product provides either enhanced effectiveness, safety, consumer acceptance, or improved quality or formulation. Category I active ingredients of the same therapeutic category may be combined if each active ingredient is present in full therapeutic doses or in subtherapeutic doses where a subtherapeutic dose is appropriate. The combination product must meet the OTC drug combination policy as cited above (21 CFR 330.10(a)(4)(iv)) in all respects and must be equal to or superior to each of the active ingredients used alone at full therapeutic doses when considered from the standpoint on a benefit-to-risk ratio. When it is not known or it has not been shown and data have not been presented that the foregoing conditions exist, the combination should not be placed in Category I.

An ingredient claimed to be a pharmacologic adjuvant will be considered an active ingredient and may be included in addition to one or more principal active ingredients only if it meets the combintion policy in all respects.

When there are data available indicating that a particular ingredient in a given combination is appropriate for use only in that combination, but is not in Category I as a single active ingredient, such an ingredient will be placed in Category I for use only when used in that particular combination.

Many combinations of oral health care products intended to be used in the mouth and throat have been in the marketplace for many years. Many of

these products continue to be used for self-medication for various clinical conditions and symptoms, even though use for these conditions has been supplanted, for the most part, by other more effective or safer drugs and methods of treatment. The Panel feels that both the OTC drug review regulations (21 CFR Part 330) and the historical evidence for the use of these combination products do not support the concept that the long-time use of an OTC product with apparent beneficial results based on impressions by consumers or without complaints of adverse reactions attest to their safety and effectiveness. The Panel is not impressed by statements appearing in some submissions, such as "marketing experience has been favorable" or "no complaints have been reported." The Panel considers marketing experience data and frequency of customer complaints to be of interest and gives them their due consideration but does not consider such data to be the type of proof that is meaningful in a scientific review of standards for existing OTC products. The paucity or lack of reports of adverse reactions are merely negative findings and are not indications or evidence of the fact that adverse reactions have not occurred. Negative findings from marketing data do not constitute a sound basis for establishing the safety and effectiveness of a product. Furthermore, most of the submissions do not describe the manner in which the data were collected from the users of these products or the instructions provided the users to facilitate and assure that all necessary meaningful data would be forthcoming in reporting adverse reactions. Very few of the submissions describe how and by whom the data were collected and interpreted or otherwise explain pertinent significant details concerning their methods of adverse reaction reporting.

The Panel, therefore, does not feel that the continued availability and use of a combination product is justified simply because such combinations have had an extensive, apparently successful marketing history.

The Panel is aware of the lack of controlled studies in the area of certain combinations used in the mouth and throat. Most studies of these types of products are of necessity of a subjective nature. Controlled clinical studies are difficult to perform, particularly for symptoms which are frequently evanescent and usually self-limited. The Panel is also aware that it is not always possible to interest investigators in such studies. The Panel agrees with FDA's conclusions of concerning difficulties in performing controlled clinical studies to determine the safety and effectiveness of these products which were published in the **Federal Register** on November 12, 1973 (38 FR 31261):

> The FDA recognizes that OTC studies are often more difficult to undertake than those involving prescription drugs. OTC drug studies are principally concerned with measuring symptomatic relief requiring methods that are more subjective than those used to measure the resolution of a diseased condition. In all cases, however, such tests are entirely feasible and indeed may have, in many cases, been conducted in the past. Nor is difficulty in performing studies sufficient justification for retaining on the market drugs, the safety and effectiveness of which are inadequately documented.

2. *Requirement of contribution.* The Panel has determined that each claimed active ingredient in a combination must make a contribution to the claimed therapeutic effect. The amount of ingredient present in a product intended for use in the oral cavity must be at least equal to the currently accepted minimum dose level for such active ingredients as required in the ingredient statements below unless data are presented to show that a lower minimum dose is adequate to achieve the intended therapeutic effect.

In its consideration of active ingredients, the Panel reviewed the safety and effectiveness of all the combinations submitted. All combinations that meet the criteria for Category I as set forth below are considered safe and effective.

The Panel considers it important that the minimum effective dose be established for each ingredient in a combination product. Where lacking, data should be developed by appropriate, well-controlled clinical studies to demonstrate the effectiveness of a dosage level.

Each claimed active ingredient in an oral health care combination product must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient having a claimed local effect on the oral and pharyngeal mucous membranes that has not been reviewed by the Panel and consequently not found in this document, such ingredient is automatically classified as a Category II ingredient and is not generally recognized as safe and effective. Appropriate animal and human testing and prior approval by FDA is required before a product containing such an ingredient may be marketed.

The Panel considered only those combination products submitted pursuant to the notice published on July 20, 1973 in the **Federal Register** (39 FR 19444). The Panel recognizes that other combination products may be in the marketplace, but it has either no knowledge of such products or insufficient data with respect to such products to make a reasonable judgment of safety or effectiveness. Accordingly, the Panel recommends that any new combination or any presently marketed combination which claims local effects on the oral and pharyngeal mucous membranes and not submitted to this Panel could be evaluated through the new drug procedures or be the subject of an appropriate petition to FDA to review or amend the OTC oral cavity drug monograph.

3. *Standards for determining Category I Combinations*—a. *Combinations of ingredients from different therapeutic categories.* Combinations of ingredients from different therapeutic categories must be limited to Category I oral health care ingredients in the dosage range specified for Category I ingredients in the ingredient satements. The following combinations are classified as Category I:

(1) One Category I topical anesthetic/analgesic may be combined with one Category I antimicrobial active ingredient. The topical anesthetic/analgesic relieves pain while the antimicrobial active ingredient is acting on the oral microorganisms. The majority of antimicrobial ingredients reviewed by the Panel are not anesthetic/analgesic ingredients and do not relieve pain.

(2) One Category I demulcent active ingredient may be combined with one Category I antimicrobial active ingrdient. The demulcent provides a soothing effect while the antimicrobial agent is acting on the oral microoganisms.

(3) One Category I decongestant active ingredient may be combined with one Category I antimicrobial active ingredient. This combination is rational because the decongestant may help reduce the edema while the antimicrobial agent is acting on the oral microorganisms.

(4) One Category I astringent may be combined with one Category I antimicrobial active ingredient because astringents provide a protective coat on ulcerated areas and aid in relieving discomfort while the antimicrobial agent is acting on the oral microorganisms.

(5) One Category I anesthetic/analgesic active ingredient may be combined with one Category I demulcent active ingredient. The anesthetic/analgesic relieves pain and the demulcent may augment this effect

by acting as a protectant and minimizing effects of external stimuli.

(6) One Category I anesthetic/analgesic active ingredient may be combined with one Category I decongestant active ingredient. The anesthetic/analgesic relieves pain by suppressing the pain receiptors, and the decongestant reduces swelling that may be stimulating pain receptors.

(7) One Category I anesthetic/analgesic active ingredient may be combined with one Category I demulcent active ingredient and with one Category I antimicrobial active ingredient. The anesthetic/analgesic relieves pain by supressing the pain receptors. The demulcent reduces the degree of stimulation of the pain receiptor on a surface lesion, while the antimicrobial ingredient is acting on the oral microorganisms.

(8) One Category I anesthetic/analgesic active ingredient may be combined with one Category I Astringent active ingredient. The anesthetic/analgesic relieves pain by supressing the pain receptors, and the astringent acts as a coagulant and provides a protective coating for a surface lesion, theregy reducing the number of stimuli affecting that area.

(9) One Category I anesthetic/analgesic active ingredient may be combined with one Category I astringent active ingredient and the one Category I antimicrobial active ingredient. The anesthetic/analgesic relieves pain by suppressing the pain receptors, and the astringent acts as a coagulant providing a protective coating for a surface lesion, thereby reducing the number of stimuli affecting that area. The antimicrobial agent acts on the oral microorganisms.

(10) One Category I anesthetic/analgesic active ingredient may be combined with one Category I decongestant active ingredient and with one Category I antimicrobial active ingredient. The anesthetic/analgesic relieves pain by suppressing the pain receptors. The decongestant helps reduce the edema, and the antimicrobial agent acts on the oral microorganisms.

b. *Combinations of ingredients from the same therapeutic category.* Category I active ingredients of the same therapeutic category but having different pharmacologic mechanisms of action and those that have the same action may be combined if each active ingredient is present in full therapeutic doses or subtherapeutic doses where a subtherapeutic dose is appropriate, but only where there is a clear demonstration that there is an improvement of safety or enhanced effectiveness or both.

4. *Standards for determining Category II combination products.* A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe and effective, if any of the following apply:

a. The combination contains any Category II ingredients or any ingredient is present above the maximum dose range for that ingredient allowed in the ingredient statement in this document.

b. One or more antimicrobial active ingredients are combined with one or more expectorant active ingredients, because the expectorant would dilute or diminish the time of contact of the antimicrobial drug with the diseased surface.

c. One or more antimicrobial ingredients are combined with any debriding active ingredients because a debriding agent would dilute or wash away the agent from the diseased surface.

d. One or more antimicrobial active ingredients are combined with an expectorant and one debriding agent because the duration of contact would be decreased or the drug washed away from the mucous surface.

e. One or more anesthetic active ingredients are combined with one debriding active ingredient because the anesthetic would be washed away, diluted, or mixed with the debris.

f. One or more anesthetic active ingredients are combined with one or more expectorants because the drug would be diluted and removed from the site of action.

g. One or more anesthetic active ingredients are combined with one or more expectorants, combined with one or more debriding agents because the anesthetic agent would be diluted or removed from the diseased site.

h. One or more active astringents are combined with one or more debriding agents because the debriding agent would prevent the astringents from exerting its coagulating effect.

i. One of more active astringents are combined with one or more expectorants because the expectorant would dilute and wash away the astringent and prevent it from acting as a coagulant.

j. One or more active astringents are combined with one or more expectorants and one or more debriding agents because the astringent would be diluted or washed away or otherwise be prevented from exerting its coagulating effect.

k. One or more decongestants are combined with one or more expectorants because the expectorant would dilute or otherwise prevent the decongestant from exerting its therapeutic effect.

l. One or more decongestants are combined with one or more expectorants, combined with one or more debriding agents because the debriding agent and the expectorant would dilute or wash away the decongestant or otherwise prevent it from exerting its therapeutic effect.

5. *Standards for determining Category III combinations.* A combination is classified as a Category III combination if any of the following apply:

a. Any Category I ingredient is below the minimum effective dose set by the Panel as found elsewhere in this document for such respective ingredient, except that Category I active ingredients of the same therapeutic category but having different pharmacologic mechanisms of action, and those that have the same action, may be combined if each active ingredient is present in full therapeutic doses or subtherapeutic doses where a subtherapeutic dose is appropriate but only where there is a clear demonstration that there is an improvement of safety or enhanced effectiveness or both.

b. One or more ingredients are Category III ingredients, as set forth elsewhere in this document for single active oral health care product ingredients.

c. A combination of two or more Category I active ingredients from the same pharmacologic class or from different pharmacologic classes but exerting similar therapeutic effects has not been shown to possess a therapeutic advantage, i.e., enhanced effectiveness, safety, consumer acceptance, or improved quality of formulation greater than each active ingredient used alone at full therapeutic doses.

6. *Requirements for the reclassification of Category III combinations to Category I combinations*—a. *Combinations with ingredients below minimum effective levels.* For any Category III combination where one or more ingredients fall below the minimum effective level as set forth elsewhere in this document for such individual ingredients, tests must be performed to substantiate the effectiveness of any such ingredient. The Panel recommends a petition to the agency for appropriate modification of the monograph to permit such lower dosages, or that testing be pursued under the NDA procedures.

b. *Combinations containing Category III ingredients.* Any combination that contains one or more ingredients in Category III, as set forth elsewhere in this document, must be tested to satisfy

Category I requirements for each such ingredient.

7. *Inactive ingredients.* The Panel recommends that a review panel be appointed to review the inactive ingredients in OTC products for the purpose of determining which of these inactive ingredients should be listed on the label.

**III. Anesthetics/Analgesics**

*A. General Discussion.*

1. *Modes of action.* Topical anesthetics/analgesics act in one or a combination of the following ways:

a. They may penetrate the epithelial barriers of the mucous membranes and completely block the receptors for the perception of pain. Such ingredients penetrate the nerve endings and cause a temporary reversible change in the nerve membrane that prevents the development of the electrical current that transmits sensory impulses along a nerve. When this occurs, a complete loss of perception of stimuli such as pinprick, touch, warmth, cold, and pressure results. When the blockade is complete, the anesthetics may induce the subjective sensation of numbness. This lack of sensation and response to pain is called anesthesia (without feeling) (Ref. 1).

b. Topical anesthetics/analgesics may act by partially blocking the transmission of impulses from the receptors for pain so that subminimal stimuli that elicit the sensation are no longer able to do so. However, the receptors are still able to respond to stronger stimuli that induce pain. This type of response is noted after application of these ingredients in dilute form so that the smaller C-type pain-carrying fibers are blocked but the larger A-type fibers are not. Ingredients acting in this manner generally do not induce the sensation of numbness. The sensations of cold, warmth, touch, or pressure usually remain undisturbed. For this reason, such ingredients are called analgesics. In this report the term "anesthetic/analgesic" is used. It should be emphasized that anesthetics in smaller doses will act as analgesics and not produce numbness. An analgesic, on the other hand, will not produce anesthesia when the dosage is increased, but might produce toxic reactions.

c. Some topical anesthetics/analgesics may penetrate the mucous membranes and exert an anti-inflammatory effect when they come into contact with a disease process that is causing discomfort in the mucous membranes. Such ingredients do not act upon receptors and nerve fibers to block transmission of impulses. They may reduce swelling in tissues by acting as antagonists to agents causing inflammation, thereby eliminating noxious stimuli that cause pain. Relief from the discomfort will require time because the anti-inflammatory effects occur gradually and are not immediately apparent. The salicylates exert anti-inflammatory effects when ingested orally. Other salicyclates and other mild anesthetics/analgesics such as antipyrine do not cause a blockade in nerve tissues.

d. Topical anesthetics/analgesics may act antagonistically to biologic agents stored in certain cells in the body. When released into the tissues by trauma or some pathologic mechanism, these agents cause cellular injury. Histamine, serotonin, various kinins, prostaglandins, etc., are stored in mast cells or white blood cells. When released into tissues where they are not ordinarily found, they exert a vasoactive effect and produce an inflammatory swelling of the cells or another not clearly understood response that results in discomfort and pain. The histamine response is characterized by swelling of the tissues, engorgement of blood vessels, and escape of fluid from the blood vessels into tissue spaces. Topical anesthetic/analgesic ingredients that antagonize the effects of histamine are called antihistamines.

e. Topical anesthetic/analgesic ingredients provide temporary symptomatic relief and are not curative. Salicylates and antihistamines may ameliorate a disease process. Relief of symptoms beyond the time the medicine exerts its topical anesthetic/analgesic effect sometimes occurs from the use of agents that directly or indirectly decrease or overcome muscle spasm, reduce edema, or alter the degree of blood flow in an affected area. Exactly how this comes about is not known.

Topical anesthetics/analgesics are applied to the mucous membranes to lessen or completely abolish pain. They act by completely blocking pain receptors resulting in a sensation of numbness and abolition of responses to painful stimuli. In some instances, not all the pain fibers are completely blocked. The smaller, unmyelinated (unsheathed) C fibers that carry the sensation of dull, aching pain are more easily blocked than the large delta A myelinated (sheathed) fibers which carry the sensation of sharp pain. Only a partial reduction in the response to painful stimuli results, but it is sufficient to alleviate discomfort of the dull, aching type of pain if the C fibers are blocked. This partial relief is rightfully called "analgesia." If all the fibers in a nerve are blocked, and no response occurs to painful stimuli, the sensation of numbness results. This is rightfully called "anesthesia." In this report, the active ingredients which produce either analgesia or anesthesia are called "anesthetics/analgesics."

2. *Chemical classification of anesthetics.* Topical anesthetics used in the mouth and throat fall into two chemical groups. One group is the nitrogen-containing amino type of anesthetics, and the other group is the hydroxy or alcohol type (Ref. 2).

The nitrogenous types are closely allied to ammonia, since the hydrogen atoms of ammonia are substituted by organic radicals. They form weak bases when dissolved in water and, like ammonium hydroxide which forms when ammonia is dissolved in water, are poorly ionized.

The solubility of the bases of nitrogenous anesthetics in water varies. Aqueous solutions of amines are alkaline. These basic compounds form salts when combined with acids just as ammonium hydroxide does when it is mixed with an acid to form a salt. The salts formed when amines combined with acids are far more soluble in water than the bases. They are also more stable. The un-ionized base is the physiologically active form of the compound.

Exactly how these ingredients exert their physiological effect is not known, but it is believed that they change the pore size on the axonal membrane and distort the channels for passage of the sodium ion from the extracellular fluid around an axon (the core of the nerve fiber) and prevent depolarization of the axonal membrane. This process has been referred to as stabilization of the membrane. The electrical impulse generated proximally at an unaffected part of a nerve cannot pass the affected area. The action of topical anesthetics is reversible and no permanent change results in the membrane. Salts of topical anesthetics are ineffective in producing a blockade because they are highly ionized and do not penetrate lipid membranes easily. However, when they are injected into tissues perineurally or applied on the mucous membranes, they are converted to the basic form because of the buffering action of the tissues. The salts, therefore, are effective topically on mucous membranes unless an excess is used. If an excess is applied, enough acid is liberated to neutralize the bases in the buffers, nullifying their effects.

The nitrogen-containing topical anesthetics are subdivided into several chemical types. These are described in more detail below. A particular

chemical configuration appears in the majority of the nitrogenous type of topical anesthetics. This configuration is composed of a hydrocarbon nucleus (benzene ring) and a nitrogen atom in the form of a tertiary amine, between which is interprosed an intervening two-carbon chain, often called the pivot. These amines are the most potent, effective, and serviceable topical anesthetics. They are also the most toxic systemically if they gain access to the bloodstream. The most effective and potent drugs have an ester or amide group linking the pivot to the hydrocarbon nucleus. Benzocaine, butamben, cocaine, and tetracaine are esters. Benzocaine is the most widely used type of ester in OTC products. The amide type of this topical anesthetic consists of a benzene ring linked to the two-carbon chain by an amide group. The end of the two-carbon chain also carries the tertiary amino group, as is the case with the ester type. Lidocaine and dibucaine are other amides that have been proposed for OTC use in the oral cavity.

The nitrogenous topical anesthetics are polar substances. The benzene ring, often called the aromatic portion, is called the lipophilic pole since it is oriented toward lipid (fatty) materials in nerve cells or the axon since nerve tissues are, relatively speaking, rich in fatty materials. The water-soluble or hydrophilic amino pole is directly opposite to the aromatic pole separated by the carbon chain. This amino pole becomes oriented into the watery phase of a medium, a cell, or cell membrane. Thus, to be effective, topical anesthetics should be sufficiently lipid soluble to penetrate lipid barriers and sufficiently water soluble to be transported to the cell

The generic names of most topical anesthetics end with the suffix "caine." The "caine" type of compounds are subdivided into two types, the water-soluble (tetracaine, lidocaine) type and the "insoluble" derivatives (benzocaine, orthoform, butamben). The so-called "insoluble" anesthetics are poorly soluble in water but are lipid soluble. However, they are not totally insoluble or they would not be effective since they would not be transmitted to the cells (Refs. 2 and 3). Because of their low degree of water solubility, they have low systemic toxicity since they are not readily absorbed and do not readily pass into the blood to accumulate to toxic levels. The highly water-soluble compounds are readily absorbed from the mucous membranes. When applied in excessive quantities, they may be absorbed so rapidly that toxic plasma levels result that can cause life-threatening or even fatal reactions. The systemic effects of these topical anesthetics are unwanted. The topical effect is the desirable effect. As long as these drugs remain in the area of the nerve endings and nerve trunks and pass slowly from the tissue fluids into the bloodstream, the amount circulating in the blood is insignificant and causes no systemic reaction (Ref. 4). In some cases the amount of drug that produces diminished sensation systemically is 500 or 600 times greater than an effective topical dose. An amount of drug which is 500 or 600 times greater than that which is effective topically can be fatal. Systemic reactions are characterized initially by stimulation of the nervous system and are manifested by convulsions. The convulsions are due to depression of the inhibitory neurons in the motor cortex. The excitatory neurons remain active. If the plasma concentration is increased still more, the excitatory neurons, in turn, are depressed. The reaction that follows is cerebral depression characterized by coma, paralysis, and cessation of respiration.

In addition, "caine" type anesthetics also depress the cardiovascular system, acting on both the heart and blood vessels. They depress conduction in the heart and disturb its rhythm and also reduce cardiac output. In addition, "caine" type anesthetics relax the blood vessels resulting in a decrease in blood pressure. The effects on the heart can occur simultaneously with the effects on the central nervous system. The systemic reactions, therefore, are of two types and are referred to as the "central nervous system type" and the "cardiovascular type." Generally, the central nervous system type of reaction is the more prominent and occurs first. These two types of systemic reactions occur from time to time following the use of these ingredients as prescription products.

The Panel considers the majority of these topical anesthetic/analgesic ingredients as unsafe for OTC use and has classified most of them as Category II. Benzocaine, however, due to its low water solubility and barely detectable blood level, does not cause systemic reactions. For this reason, it is one of the safest, least toxic, and most effective of the "caine" type anesthetics (Refs. 5 and 6).

Of all the nitrogen-containing topical anesthetics used in OTC products, many are of the "caine" type; however, there are nitrogen-containing topical anesthetics used in OTC products which are not of the "caine" type. Some have structures that are modifications of this classical chemical configuration characteristic of the "caine" class of drugs (Ref. 2). The aromatic nucleus may be attached to the remainder of the molecule by a ketone, ether, or other type of linkage instead of the ester and amide type (Ref. 2). The two-carbon chain may have side chains. The names of these types of derivatives usually bear the suffix "-ine" instead of "-caine." Pramoxine and dyclonine are nitrogen-containing compounds that are examples of non-"caine" type drugs. Their molecules are modified sufficiently so that they are effective as topical anesthetics; if they are absorbed, they may produce systemic responses but not of the severity of those which are characteristic of the "caines." These non-"caine" anesthetics are irritating and may cause sloughing. They are not effective when injected perineurally, but are effective when applied topically on the mucous membranes. Therefore, they are used topically, but are not suitable for injection. They do not cause convulsions, but some non-"caine" anesthetics may cause cardiac depression.

Some antihistamines have structures that are modifications of the "caine" type of topical anesthetics. They possess, in addition to the antihistamine effect, a topical anesthetic effect as well (Refs. 1 and 2). Their names bear the suffix "-ine" also. Some antihistamines are suitable topically for anesthesia, but not for injection (Ref. 2). These are described below.

The second type of topical anesthetic mentioned above, the alcohol or hydroxy type, consists of non-nitrogenous compounds. The alcohol-type drugs, such as phenol, benzyl alcohol, hexylresorcinol, and salicyl alcohol do not cause central nervous system or cardiovascular effects characteristic of the "caine" type drugs. The alcohols may be cyclic, aliphatic, or aromatic. Some of the drugs in the volatile oil group, such as menthol, camphor, and other cyclic alcohols, have topical anesthetic action. Systemic effects, if they occur, vary with the individual compound. Alcohol-type anesthetics are effective when applied topically, but produce neurolysis when injected perineurally. The hydroxy compounds are polar substances and are believed to orient into the cell membrane in the same manner as the nitrogen-containing compounds. They possess varying degrees of lipid solubility. Their action does not depend upon pH as is the case with the nitrogen-containing compounds. They

are readily absorbed through the mucous membranes and intact skin.

The "water-insoluble" esters, such as benzocaine and butamben, which are considered to be "caine" type drugs, are not absorbed in sufficient quantities to produce plasma levels that cause systemic reactions and, therefore, are relatively safe. Convulsions and cardiac depression do not occur from the use of these types of compounds. These have been used as anesthetics in oral health care products without any serious toxic effects. They are effective on the mucous membranes, the poor water solubility notwithstanding. They are soluble in glycols and other similar water-soluble bases and are readily applied in effective concentrations, in the form of rinses or sprays, to the mucous membranes of the mouth and throat. Bioactive quantities are delivered to paid receptors when solutions prepared with these solvents are applied to a surface. The degree of anesthesia that results depends upon the quantity used.

Topical anesthetics readily traverse the epithelial barriers of the mucous membranes and pass into the tissue fluids beneath, into the venules and lymphatics and are then distributed to various tissues, particularly those that are capillary-rich. Some esters of para-aminobenzoic acid, such as tetracaine and benzocaine, are hydrolyzed by plasma esterases into the alcohol and acid from which they were formed and thereby inactivated. The portions that are not metabolized in the blood are inactivated by the liver. The amide type of topical anesthetic is not hydrolyzed by esterases, but ultimately passes from the blood and tissues to the liver when it undergoes biodegradation (detoxification) through various metabolic pathways, such as oxidation, reduction, etc. The byproducts are eliminated in the urine.

Topical anesthetics, such as dibucaine and cocaine, that are not hydrolyzed by plasma esterases are not detoxified by the liver and are eliminated unchanged by the kidney. The alcohol type of topical anesthetic is not affected by the plasma esterases. Such anesthetics are detoxified by the liver by various types of chemical reactions, such as oxidation, reduction, hydrolysis, conjugation, or transfer reactions. Unmetabolized portions are excreted in the urine. Solvents and other substances used to formulate a finished product that penetrates the epithelial barriers are detoxified in the same manner as the active ingredients. It is possible for highly lipophilic substances that are used daily, for long periods of time, particularly if they are not readily biodegradable, to accumulate in the adipose and other lipid-rich tissues where they remain for days, weeks, or months depending upon their half-lives in the body. None of the ingredients the Panel has evaluated are retained for long periods of time in adipose or lipid-rich tissues.

Antihistamines and other topical anesthetic drugs not fitting into the "caine" type or derivatives related to the "caine" categories described above are absorbed, distributed, metabolized, and excreted in the same manner as those described above. In many cases, the exact metabolic fate is not known. Antihistamines are discussed in detail below. (See part III. paragraph A.3. below—Antihistamines used as anesthetics in the oral cavity.)

When two of the "caine" type of topical anesthetics are combined, they act additively as far as systemic toxicity is concerned. Adriani and Zepernick (Ref. 7) showed that if half of a dose of lidocaine that causes central nervous system excitation manifested by seizures is combined with half of the dose of tetracaine that does the same, intravenously in a dog, the two act additively and cause seizures. They also showed that when equal volumes of aqueous solutions of lidocaine and tetracaine in concentrations that produce the maximal topical effect on the mucous membranes beyond which no further benefit is gained by increasing the concentrations are combined, the duration of action of the combination is that of the longer-lasting drug (Ref. 7). Combining the two drugs does not increase the duration of anesthesia. The latent period, i.e., the time interval between the moment of application of the drug and the moment the anesthesia is perceived, is the same as that of the shorter-acting drug.

These topical anesthetics can produce a complete blockade and anesthesia that abolish reflex activity in the pharynx and larynx. This degree of blockade is necessary for completion of endoscopic or other surgical procedures. The drug does not penetrate beyond the mucous membranes; therefore, surgery of deeper structures cannot be performed by using topical anesthesia. In the treatment of painful disorders of the mouth, this degree of blockade is not required and is undesirable since there is a possibility that loss of gag and laryngeal reflexes might lead to aspiration of secretions, food, and other foreign substances. Aspiration under these circumstances is more of a possibility in subjects who have difficulty in swallowing due to neurological diseases, muscle dystrophies, or in elderly subjects in whom the gag reflexes are decreased in activity. Doty and Bosma (Ref. 8) have shown that application of cocaine or lidocaine respectively does not alter the swallowing reflex. With drugs such as benzocaine and benzyl alcohol, the minimum effective anesthetic concentration is advocated. Only a partial blockade is sought and induced. These drugs are administered in the oral cavity in the form of lozenges which are slowly dissolved in the mouth so that a continuous bathing of the mucous membranes occurs. The quantity released from the lozenge should be sufficient to alleviate discomfort, but it should not be so great as to produce a complete loss of reflexes and numbness.

The salicylates and chemically and pharmacologically related "analgesics," such as aspirin and antipyrine, have been advocated for use topically to relieve painful conditions in the mouth and throat. Neither the salicylates nor other analgesics block the neuronal membranes as do the topical anesthetics.

3. *Antihistamines used as anesthetics/analgesics in the oral cavity.* Antihistamines are drugs that act competitively with histamine. They are polar substances that have an amino group which becomes attached to receptors for histamine. Their structural configuration resembles the nitrogen-containing topical anesthetics in many respects. They possess one or more amino groups, are bases, and form salts with acids. Some antihistamines such as tripelennamine, are derived from ethylenediamine, and other antihistamines, such as diphenhydramine are derived from ethanolamine. The salts are highly ionized, poorly water soluble, and are not lipophilic. The bases are lipophilic and poorly ionized. Their absorption through the mucous membranes is similar to that of the "caine" and related nitrogen-containing topical anesthetics. Even though the structure of antihistamines, in may respects, resembles the general configuration characteristic of the "caine" type of topical anesthetic drugs, there is sufficient modification so that they do not manifest systemic effects similar to the "caine" drugs when they pass into the circulation.

The actions of antihistamines overlap with those of other drugs. Some have anticholinergic, antinauseant, and topical anesthetic activity. They act as anti-inflammatory agents when the inflammation is due to histamine release. Antihistamines that have

topical anesthetic/analgesic activity may be useful for relieving pain in preparations used in the oral cavity. There is little evidence that they are effective topically as antihistaminics. Any beneficial effects that may result are most likely due to the systemic effect from absorption from the mucous membranes of the mouth or throat or to any part of a dose that is swallowed. The antihistamines are furmulated as salts, such as the hydrochlorides. The buffering action converts the salts to the base form which is the active form. The base penetrates the mucous membranes and is easily absorbed. Most of the effects of a histamine are systemic. Some antihistamines have pronounced sedative effects and may cause drowsiness if used topically in oral health care preparations since they are absorbed and act systemically. Some have a central stimulating action, but this is not pronounced except in cases of overdosage.

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*B. Categorization of Data*

1. *Category I conditions under which oral health care anesthetic/analgesic agents for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register**.

*Category I Active Ingredients.*

Aspirin
Benzocaine
Benzyl alcohol
Dyclonine hydrochloride
Hexylresorcinol
Menthol
Phenol
Phenolate sodium
Salicyl alcohol

a. *Aspirin.* The Panel disagreed on important issues relevant to the safety and effectiveness of aspirin. Accordingly, part III, paragraph B.1.a.—Aspirin—consists of a majority report and a minority report. The minority report reflects the opinion of one Panel member.

(1) *Majority report on aspirin.* The Panel concludes that aspirin is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Aspirin is the acetyl ester of salicylic acid (acetylsalicylic acid) (Ref. 1). Acetylsalicylic acid had been synthesized in 1899 by Dreser some years before it was introduced into medicine. It was first known as acetyl spiricum, from which the name aspirin is derived. Originally, it was obtained from a plant source, *Spiraea ulmaria.*

Aspirin is made by interacting acetic acid with salicylic acid. The acetic acid interacts with the hydroxyl group on the 2 position of salicylic acid. Aspirin is an odorless powder consisting of white, tubular or needlelike crystals (mostly monoclinic crystals, but orthorhombic and trichlinic crystals are at times encountered). It melts at approximately 135° C. In moist air, it is gradually hydrolyzed into salicylic and acetic acids and acquires the odor of acetic acid. It is stable in dry air (Ref. 2).

The dissolution of aspirin is a conditional process depending on the temperature of the water. One gram (g) dissolves in 300 mL water at 25° C, 100 mL water at 37° C (one 300-mg tablet of aspirin dissolves in 30 mL water at 37° C), 5 mL alcohol, 17 mL chloroform and 10 to 15 mL ether. When a commercially available aspirin tablet is dissolved (within the ratio mentioned above) the resulting fluid has the appearance of a suspension. Actually only the filler and binder are in suspension, while the acetylsalicylic acid is in solution. The filler can be separated by sedimentation and decantation or by filtration. When the remaining fluid is allowed to evaporate, the typical aspirin crystals will be obtained. When aspirin without filler is dissolved, the resulting fluid is clear. Evaporation will produce the typical aspirin crystals. Once the aspirin is in solution it will resist separation or crystallization when the temperature is lowered. No crystallization was observed when the aspirin solution was kept at −7° C for 16 hours (Ref. 3). It is decomposed by boiling water or when dissolved in solutions of alkali hydroxides and carbonates. Inorganic salts of acetylsalicylic acid are soluble in water, but are decomposed quickly (Ref. 4). Two polymorphic forms have been described. One form is prepared from a slow crystallization process at room temperature from a saturated solution of aspirin in 95 percent alcohol. This form melts between 143° and 144° C. The other form melts between 123° and 125° C. Tablets prepared from the product derived from the slow crystallization technique have a slower rate of dissolution than tablets prepared from the latter type of polymorph. There is evidence from the study of these two forms that aspirin crystals are converted to the less soluble form during dissolution. The study of aspirin in aqueous media has led to the suggestion that a phase change occurs on the surface of the crystals (Ref. 1).

Aspirin readily undergoes hydrolysis in aqueous solutions with the liberation of salicylic and acetic acids. In pure water complete decomposition takes place in 100 days. Acids hasten the rate of hydrolysis. The alkalis present in solutions of alkaline acetate and citrate dissolve aspirin, but the resulting solutions hydrolyze rapidly to form salts of acetic and salicylic acids. Half the aspirin decomposes in about 4 days. The decomposition may be retracted somewhat by glycerin and sugar. Liquefaction occurs when aspirin is saturated with phenyl salicylate, acetanilid, phenacetin, aminopyrine, antipyrine, and other organic products. Partial hydrolysis occurs in mixtures of aspirin and hygroscopic substances of salts containing water of hydration. Even some talcs adversely effect the stability of aspirin (Ref. 5).

(i) *Safety.* The Panel concludes that aspirin is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Aspirin applied topically to the skin is neither an irritant nor a counterirritant. However, it is irritating to the mucous membranes of the mouth and throat when the solid form is kept in contact with the mucosa for any length of time, either by design or accident. This has been known practically since the introduction of aspirin and is a well-established fact. Kawashima, Flagg, and Cox (Ref. 6) reported a case where

ulceration of the mucosa of the roof of the mouth resulted from the application of a tablet of aspirin by the patient for pain relief. The lesion healed promptly after aspirin medication was stopped. Roth et al. (Ref. 7) found that aspirin tablets remaining in contact with the roof of the mouth for one-half hour produced white, opaque buccal mucosal lesions which could be peeled off with slight pressure or by rubbing. They placed a quarter of a tablet each of plain, buffered, and combination tablets between the lower lip and the gum of 26 normal subjects for 30 to 60 minutes. The aspirin produced irregular lesions of sloughing and superficial necrosis of the mucous membranes of the mouth. In contrast to these observations, when a disc of cottonoid, 13 millimeters (mm) in diameter, saturated with a solution of aspirin without filler is placed on the mucosa of the lower lip and kept there for 60 minutes, no blanching of the mucosa or ulcerations was observed (Ref. 3). This procedure was repeated on 3 consecutive days, using approximately the same location, again without blanching or ulcerations. Reports of ulcerations with the use of aspirin-containing chewing gum could not be found. Ulcerations are, of course, also a possibility with this type of medication.

Aspirin has a free carboxyl group, but it is a weak acid. Aspirin is poorly absorbed from the mouth, but it is readily absorbed from the stomach since it is nonionized in this form. In the intestines, it is absorbed as the acetylsalicylate ion. Peak serum levels are reached in 1 to 2 hours after oral ingestion. Blood levels do not necessarily correlate with the degree of analgesia. Half or more of the blood-borne aspirin is bound to plasma proteins, especially albumin, by means of the carboxyl group. The drug is very rapidly distributed to all body tissues. It is excreted very rapidly, although traces continue to be excreted for several days. In febrile patients, a proportion is eliminated unchanged, to some extent, but most is converted to salicyluric acid. Smaller amounts of the drug are eliminated as salicylic acid and also as conjugates with glucuronic acid to form glucuronates. Some of the drug is eliminated as gentisic acid.

Aspirin is not highly toxic when taken orally or given parenterally notwithstanding the voluminous literature on poisoning by the drug. When the widespread use of aspirin is taken into consideration, the total number of cases of poisoning that occur is small when they are extrapolated to the number of doses used. A single dose of 10 to 30 g aspirin may be fatal in an adult, although less than 1 g aspirin has killed and 130 g have been tolerated (Ref. 8). Children (especially under the age of 3 years) are disproportionately more susceptible than adults to the toxic action of salicylates (Ref. 9). Impaired renal function accentuates toxicity.

A total of 12 g ingested during 24 hours usually produces symptoms of salicylism, i.e., tinnitus, vertigo, impaired hearing, and headache. More severe manifestations include hyperpnea, fever, metabolic acidosis, and, less regularly, dimness of vision, sweating, thirst, vomiting, gastrointestinal hemorrhage, diarrhea, skin rashes, tachycardia, restlessness and delirium, depression, stupor, coma, cardiovascular collapse, convulsions, and respiratory failure. Fatal cases show diffuse endothelial changes with petechial hemorrhages and congestion through the viscera (Ref. 10).

One of the untoward effects following oral administration of aspirin is its propensity to cause bleeding, particularly of the gastric mucosa. The extent of blood loss from the stomach is dose related. This effect, which reportedly occurs in 70 percent of the patients taking repeated doses of aspirin, has been studied by determining the fecal blood loss in healthy human volunteers injected with radioactive chromium-51 tagged red blood cells (Ref. 11). The radioactivity of the stools provided data which were used to plot the amount of blood loss. Prior to administration of 0.3 g aspirin, the average daily blood loss in a group of volunteers was 0.3 mL per individual. With doses of aspirin of 2.6 g daily, the average loss was increased to 2.3 mL per individual. When doses of 4.5 g aspirin were administered daily, losses increased to 6 mL per individual.

Aspirin may cause ulcerations of the mucosa of the stomach. This is believed to be due to the fact that it is un-ionized in the acid medium (pH less than 2) in the stomach and passes through the lipid barrier of the mucosal cells. Once in the cells, where the pH is close to 7, it becomes ionized and hydrolyzes to salicylic and acetic acids.

Macerations are far less frequent in the intestines because the pH is close to 7 and passage into the intestinal mucosal cells is limited, since the aspirin in the lumen is ionized. Less drug concentrates in these cells.

Since the administration of aspirin causes an increase in bleeding time from an average of 2.6 minutes during the control period to an average of 4.5 minutes when aspirin was given to the aforementioned subjects (Ref. 11), the question of whether gastrointestinal bleeding is due to the local effect on the mucosa of the stomach or to a systemic effect related in prolongation of bleeding time, has been the subject of considerable debate. That it is a local effect appears to be established by the fact that when sodium salicylate is injected intravenously, gastrointestinal bleeding does not occur. Bleeding time is prolonged to approximately the same degree whether aspirin is given orally or parenterally. The importance of recognizing this untoward effect of aspirin in patients with hemostatic abnormalities and clotting defects has been stressed and documented in many reports, although bleeding time prolongation has been ascribed to a defective vascular response. Others attribute it to a decrease in blood platelet aggregation. Following injury to a capillary, endogenous adenosine diphosphate is released from platelets causing an irreversible aggregation which results in the formation of a plug that is primarily responsible for the arrest of bleeding. Aspirin apparently inhibits the release of endogenous adenosine diphosphate, thereby prolonging bleeding time. As little as 5 g aspirin can produce this type of platelet defect, and the abnormality persists anywhere from 4 to 7 days, corresponding to the life-span of the platelets. Since aspirin is absorbed to some extent through the oral and pharygeal mucous membranes and circulates in the blood, this effect upon coagulation is of importance, particularly since it is used in mouthwashes and in chewing gum.

Late post-tonsillectomy hemorrhages have been attributed to the use of aspirin in tablet or chewing gum form, while no bleeding was seen with acetaminophen (Ref. 12).

The Panel feels that the use of aspirin orally or topically in patients who have a bleeding tendency or after dental or throat surgery may be unwarranted and recommends that a warning be placed on the label stating: "Do not use if you have a bleeding problem or after dental or throat surgery."

The exact relationship between ulcerogenic potential in the mouth and that in the stomach has not been established since the pH of saliva is below 6, while that of the gastric juice is less than 2. It is felt that the adverse reactions are basically the result of the acetyl group.

Two types of systemic adverse reactions may occur from aspirin, the idiosyncratic type and the allergic type. Idiosyncrasy to aspirin is rare. It does occur, however, and the symptoms differ from the allergic type of response. The

idiosyncratic reaction is not of the immunologic-type reaction, but is believed to be due to disturbances in prostaglandin synthesis. As is the case with any other drug, aspirin can act as a hapten and produce sensitization. Sensitization is most frequently observed in high-risk allergic (atopic) individuals, particularly in asthmatics, and especially in those with nasal polyps (Refs. 13 and 14). The manifestations of an allergic response are urticaria, erythema, desquamatative, bullous, or purpural skin lesions, angioneurotic edema, laryngeal stridor, asthma, and peripheral vascular collapse. Absorption of aspirin from mucous membranes may produce a systemic allergic response. These reactions are often serious and fatal.

In summary, then, the Panel feels that aspirin should not be used either systemically or topically following operative procedures of the mouth or throat, when the mucous membranes are highly inflamed or abraded, when there are eroded lesions that are bleeding, or when the patient is on anticoagulant medication because aspirin interferes with the clotting mechanism and bleeding may result.

(ii) *Effectiveness.* The Panel concludes that aspirin is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The Panel concludes that aspirin has a local analgesic effect in the oral cavity (Ref. 3). It is useful in relieving mild to moderate pain, not only when the pain is localized, but also when it is generalized. There is evidence that some of the pain relief obtained from orally ingested aspirin is due to a peripheral effect. Since salicylates exert an anti-inflammatory effect, part of the pain relief may be also due to preventing or reducing the inflammation and thereby removing one of the sources of the stimuli to the pain receptors. Lim et al. (Ref. 15) noted that salicylates apparently block painful stimulation of visceral receptors caused by intra-arterially or intraperitoneally injected bradykinin. They postulate that the analgesic effect is due to blockage of chemoreceptors mediating pain. Whether the salicylate effect is confined to endothelial and mesothelial structures where bradykinin may be a mediator of pain is still not known. More recent data indicate that salicylates act by preventing local inflammation not due to bradykinin (Refs. 16 through 19). Scott (Ref. 20) reports that topical application of aspirin inhibits steady-state discharge and response to a brief heat stimulus. He was able to terminate the local effect by washing the aspirin out of the dental socket.

Many diverse statements have been made regarding the mechanism of action of aspirin. This is quite understandable since aspirin has a wide range of actions. It is, therefore, necessary to state to which action reference is made. According to current knowledge, the analgesic action of aspirin is peripheral (Refs. 21 through 24) and topical (Refs. 3 and 20). The antipyretic action is central, located in the preoptic, anterior hypothalamic region (Ref. 25). The perspiration accompanying a fever is a peripheral mechanism. A local effect, in addition to the analgesic effect, is also demonstrated by desquamation and by local mucosal erosions (the so-called "aspirin burn"). Tissue damage and bleeding are significantly influenced by the general status of the patient, including such conditions as blood dyscrasia, vitamin K deficiency, anticoagulants, and alcoholism. Whether or not aspirin is actually completely dissolved will also influence tissue damage (Ref. 3). The importance of adequate fluid intake with aspirin medication cannot be stressed enough (Ref. 3).

The Panel accepts that the analgesic action of aspirin is peripheral and topical.

(iii) *Dosage.* The topical dosage of aspirin is incorporated in a chewing gum base. Adults: Chew 420 mg of aspirin as needed, not to exceed 3,360 mg in 24 hours. Children 6 to under 12 years of age: Chew 210 to 420 mg of aspirin as needed, not to exceed 1,680 mg in 24 hours. Children 3 to under 6 years of age: Chew 210 mg of aspirin as needed, not to exceed 630 mg in 24 hours. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(iv) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

In addition, the Panel recommends the following specific labeling:

*Warnings.* (*a*) "Do not use if you are sensitive or allergic to aspirin."

(*b*) "Do not use if you have a bleeding problem or if you are taking an anticoagulant drug."

(*c*) "Do not use without a physician's or dentist's advice if your mouth is highly irritated or ulcerated."

(*d*) "Do not use after surgery in the mouth or throat."

(*e*) "Provide good fluid intake when aspirin or aspirin-containing preparations are used."

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(2) *Minority report on aspirin.* The minority of the Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of aspirin as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The minority emphasizes that it is evaluating aspirin as an ingredient for topical use and is evaluating the ingredient per se and not any particular formulation.

Aspirin is the acetyl ester of salicylic acid (acetylsalicylic acid) (Ref. 1). Acetylsalicylic acid had been synthesized in 1899 by Dreser some years before it was introduced into medicine. It was first known as acetyl spiricum, from which the name aspirin is derived. Originally, it was obtained from a plant source, *Spiraea ulmaria.*

Aspirin is made by interacting acetic acid with salicylic acid. The acetic acid interacts with the hydroxyl group on the 2 position of salicylic acid. Aspirin is an odorless powder consisting of white, tubular, or needle-like cyrstals. It melts at approximately 135° C. In moist air, it slowly hydrolyzes to salicylic and acetic acids and acquires the odor of acetic acid. One gram dissolves in approximately 300 mL water at 25° C, in 100 mL at 37° C, 5 mL alcohol, 17 mL chloroform, and 10 to 15 mL ether at 25° C. Two polymorphic forms have been described. One form is prepared by a slow crystallization process at room temperature from a saturated solution of aspirin in 95 percent alcohol. This form melts between 143° and 144° C. The other form is obtained simply from evaporation of a hexane solution. It melts between 123° and 125° C. Tablets prepared from the product derived from the slow crystallization technique have a slower rate of dissolution than tablets prepared from the latter type of polymorph. There is evidence from the study of these two forms that aspirin crystals are converted to the less soluble form during dissolution. The study of aspirin in aqueous media has led to the suggestion that a phase change occurs on the surface of the crystals (Ref. 1).

Aspirin readily undergoes hydrolysis in aqueous solutions with the liberation of salicylic and acetic acids. In pure water, complete decomposition takes place in 100 days. Acids hasten the rapidity of hydrolysis. The alkalis present in solutions of alkaline acetate and citrate dissolve aspirin, but the resulting solutions hydrolyze rapidly to form salts of acetic and salicylic acids. Half the aspirin decomposes in about 4 days. The decomposition may be retarded somewhat by glycerin and sugar. Liquefaction occurs when aspirin is saturated with phenyl salicylate, acetanilid, phenacetin, aminopyrine, antipyrine, and many other organic products. Partial hydrolysis occurs in mixtures of aspirin and hydroscopic substances or salts containing water of hydration. Even some talcs adversely effect the stability of aspirin (Ref. 2). Aspirin decomposes when dissolved in solutions of alkali hydroxides and carbonates. It forms a methyl and phenyl ester and inorganic salts. Inorganic salts decompose readily when dissolved in water, especially the calcium salt. It forms a sodium salt (Ref. 3).

(i) *Safety.* The minority of the Panel concludes that there are insufficient data to classify aspirin as a safe OTC analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Aspirin applied topically to the skin is neither an irritant nor a counterirritant. However, it is irritating to all the surface mucosal cells lining the gastrointestinal tract including the mucous membranes of the mouth and throat (42 FR 3538). Kawashima, Flagg, and Cox (Ref. 4) in 1975 reported that aspirin tablets applied directly to the mucous membranes of the mouth for a local analgesic effect caused lesions of the mucous membranes of the roof of the mouth. Roth et al. (Ref. 5) found that aspirin tablets remaining in contact with the roof of the mouth for one-half hour produced white, opaque buccal mucosal lesions capable of being peeled off with slight pressue or by rubbing. They placed a quarter of a tablet of plain, buffered, and combination tablets between the lower lip and the gum of 26 normal subjects for 30 to 60 minutes. In every case the aspirin produced irregular lesions of sloughing and superficial necrosis of the mucous membranes of the mouth. Aspirin incorporated in chewing gum has produced severe lesions of the inner wall of the cheek which promptly healed when use of the preparation was discontinued (Refs. 4 and 6).

Aspirin has a free carboxyl group, but it is a weak acid which combines with metallic ions to form salts and with organic radicals to form esters, as mentioned above. Aluminum aspirin, used as an internal analgesic, is insoluable in water. Aspirin is poorly absorbed from the mouth, but it is readily absorbed from the stomach since it is nonionized in this form. In the small intestine, it is absorbed as the acetylsalicylate ion. Peak serum levels are reached in 1 to 2 hours after oral ingestion. Blood levels do not necessarily correlate with the degree of analgesia. Half or more of the blood-borne aspirin is bound to plasma proteins, especially albumin, by means of the carboxyl group. The drug is very rapidly distributed to all body tissues. Aspirin is excreted very rapidly, although traces continue to be excreted for several days. In febrile patients, a proportion is eliminated unchanged, to some extent, but most of it is converted to salicyluric acid. Smaller amounts of the drug are eliminated as salicylic acid and also as conjugates with glucuronic acid to form glucuronates. Some of the drug is eliminated as gentisic acid.

Aspirin is not highly toxic systemically when taken orally or given parenterally notwithstanding the voluminous literature on poisoning by the drug. Much of the poisoning is accidental and occurs in children. When the widespread use of aspirin is taken into consideration, the total number of cases of poisoning that occur is small when they are extrapolated to the number of doses used. A single dose of 10 to 30 g aspirin may be fatal, although survival has been reported when much

larger doses have been ingested. Deaths from smaller doses have been reported. Impaired renal function accentuates toxicity. A total of 12 g aspirin ingested during 24 hours usually produces symptoms of salicylism, i.e., tinnitus, vertigo, impaired hearing, and headache. More severe manifestations include hyperpnea, fever, metabolic acidosis, and, less regularly, dimness of vision, sweating, thirst, vomiting, diarrhea, skin rashes, tachycardia, restlessness, and delirium. Salicylism may resemble diabetic and renal disorders. Numerous cases of depression, stupor, coma, cardiovascular collapse, convulsions, and respiratory failure follow salicylism. Fatal cases show diffuse endothelial changes with petechial hemorrhages and congestion through the viscera (Ref. 7).

One of the untoward effects following oral administration of aspirin is its propensity to cause mucosal bleeding, particularly of the gastric mucosa. The extent of blood loss from the stomach is dose related. This effect, which reportedly occurs in 70 percent of patients taking repeated doses of aspirin, has been studied by determining the fecal blood loss in healthy human volunteers injected with radioactive chromium-51-tagged red blood cells. The radioactivity of the stools provided data for determinig the degree of blood loss. Prior to administration of 0.3 g aspirin, the average daily blood loss in one group of volunteers was 0.3 mL per individual. With doses of aspirin of 2.6 g daily, the average loss was increased to 2.3 mL per individual. When doses of 4.5 g aspirin were administered daily, losses increased to 6 mL per individual (Ref. 8).

Aspirin causes ulcerations of the mucosa of the stomach. This is believed to be due to the fact that it is un-ionized in the acid medium (pH less than 2) in the stomach and passes through the lipid barrier of the mucosal cells. Once in the cells, where the pH is close to 7, it becomes ionized and hydrolyzes to salicylic and acetic acids. Ulcerations occur less frequently in the intestines and on other mucosal surfaces because the pH is close to 7 and passage into the mucosal cells is limited, since the aspirin is ionized. Less drug concentrates in these cells.

The question of whether gastrointestinal bleeding is due to a local effect on the mucosa of the stomach or to a systemic effect related to prolongation of bleeding time has been the subject of considerable debate. That it is a local effect appears to be established by the fact that when aspirin as a sodium salt (not sodium salicylate) is injected intravenously, gastrointestinal bleeding does not occur. Apparently, the presence of the acetyl group is essential for this response (Ref. 9). The administration of aspirin caused an increase in bleeding time from an average of 2.6 minutes during the control period to an average of 4.5 minutes when aspirin was given to test subjects (Ref. 8). Bleeding time is prolonged to approximately the same degree whether aspirin is given orally or parenterally. This bleeding time increase is ascribed to a decrease in circulating prothrombin. It also occurs after the administration of sodium salicylate. Apparently the presence of the acetyl group is not necessary to cause prolongation of bleeding time due to hypoprothrombinemia. The importance of recognizing this untoward effect of aspirin in patients with hemostatic abnormalities and clotting defects has been stressed and documented in many reports.

Aspirin also causes a decrease in blood platelet aggregation. Following injury to a capillary, endogenous adenosine diphosphate is released from platelets causing an irreversible aggregation which results in the formation of a plug that is primarily responsible for the arrest of bleeding. Aspirin apparently inhibits the release of endogenous adenosine diphosphate, thereby prolonging bleeding time. As little as 5 g aspirin can produce this type of platelet defect and the abnormality persists anywhere from 4 to 7 days, corresponding to the life-span of the platelets. Inhibition of platelet aggregation does not occur when sodium salicylate is administered. Apparently the presence of the acetyl group is necessary for this adverse response to occur. Since aspirin is absorbed to some extent through the oral and pharyngeal mucous membranes and circulates in the blood, this effect upon coagulation is of importance particularly since it is used in gargles, chewable tablets, and in chewing gum.

Locally applied aspirin may produce massive hemorrhage from capillary beds of tissue other than that of the gastric mucosa, such as the tonsillar areas of the throat. Several cases of massive hemorrhage from the tonsillar bed following topical application of a gargle of aspirin-containing chewing gum have been reported (Refs. 10 and 11). Hemorrhage was observed in 8 percent of 100 posttonsillectomy patients medicated with aspirin (Ref. 12). The bleeding occurred on the sixth or seventh postoperative day. No bleeding occurred in 100 patients medicated with acetaminophen. A high incidence of posttonsillectomy bleeding was reported by Fox and West (Ref. 13) in children given an aspirin-containing chewing gum. The incidence of bleeding ceased when use of the gum was discontinued. Hersh (Ref. 14) noted more bleeding among patients undergoing dental extractions who received aspirin than those who received acetaminophen preoperatively.

The exact relationship between ulcerogenic potential in the mouth and that in the stomach has not been established. The pH of saliva is seldom below 6 and the aspirin is ionized and not absorbed, while that of the gastric juice is less than 2 and the aspirin is un-ionized and readily absorbed. Apparently the presence of the hydrogen ion is not essential for this reaction to occur.

The minority of the Panel feels that the use of aspirin topically or orally in patients with lesions in the mouth that may bleed may be unwarranted and recommends that a warning be placed on the labeling stating, "Do not use if you have bleeding problems."

Two types of systemic hypersensitivity reactions may occur from aspirin, the idiosyncratic type and the allergic type. Idiosyncrasy to aspirin is rare. It does occur, however, and the symptoms differ from the allergic type of response. The triad of idiosyncrasy, nasal polyps, and late onset of asthma are the usual manifestations. The idiosyncratic reaction is not an immunologic-type reaction, but is believed to be due to disturbances in prostaglandin synthesis. As is the case with any other drug, aspirin can act as a hapten and produce both systemic and local sensitization. Sensitization is most frequently observed in high-risk allergic (atopic) individuals, particularly in asthmatics (Refs. 15 and 16). The manifestations of a local sensitization are erythema, desquamatative, bullous, or purpural skin lesions. The manifestations of systemic sensitization are angioneurotic edema, laryngeal stridor, asthma, and peripheral vascular collapse. Absorption of aspirin from mucous membranes of the mouth and throat may produce any of the above responses. Some of these reactions are often serious and may be fatal. (See part II. paragraph E. above—Adverse Reactions.)

In summary then, the minority of the Panel believes that aspirin is not desirable and is not always safe and should not be used topically for symptomatic relief of conditions of the mouth and throat. The minority of the Panel feels it should not be used to treat conditions in which the mucous membranes are highly inflamed or abraded because aspirin is irritating to

mucosal surfaces. The minority of the Panel also believes that aspirin should not be used following operative procedures of the mouth or throat or for eroded lesions that are oozing blood, because the drug interferes with clotting mechansims, and bleeding may be enhanced.

(ii) *Effectiveness.* The minority of the Panel concludes that there are insufficient data available to permit final classification of the effectiveness of aspirin as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within in the proposed dosage limit set forth below.

Aspirin is the most widely used OTC internal analgesic ingredient in the United States (Ref. 9). In view of its immense popularity in this country, it has been extensively discussed in the medical and scientific literature. Aspirin is useful as a systemically acting analgesic to relieve mild to moderate pain, not only when the pain is localized, but also when it is generalized. Thousands of articles have been written concerning aspirin since the first pharmacologic data were reported in the literature in 1899.

Aspirin possesses no known topical anesthetic activity and does not block transmission of nerve impulses by altering the neuronal membranes as do topical anesthetics such as benzocaine, tetracaine, and lidocaine (Ref. 17). It, therefore, exerts no known anesthetic or analgesic effect on the skin or mucous membranes. Gargling with solutions of aspirin produces irritation and burning sensations, particularly if the solutions are concentrated, instead of a numbing effect which aspirin should do if it were a local anesthetic.

The chemical structure of aspirin in no way resembles the structure of the hydroxy or nitrogenous types of local anesthetics. Indeed, the introduction of a carboxyl group on a structure known to possess local anesthetic activity, as for example cocaine, nullifies its local anesthetic activity. Removal of the methyl group from ecgonine leaves a free carboxyl group on the structure of cocaine and nullifies its local anesthetic activity (Ref. 19). Aspirin is also nonionized at very low pH's such as that of the stomach. At the pH of the oral cavity it is ionized and would be less inclined to be absorbed and to pass through the mucous membranes of the mouth and throat and into the lipid sheath of a nerve fiber. Impulse conduction along peripheral nerves is not affected by salicylates (Ref. 17). The interference with absorption due to the fact that aspirin is ionized would negate any possibility that it acts directly to antagonize the effects of bradykinin or prostaglandins in the submucosal tissues.

Aspirin, as is the case with other internal analgesics, acts centrally at thalamic and subcortical areas. However, there is evidence that some of the pain relief obtained from orally ingested aspirin is due to a peripheral effect of the blood-borne drug (Ref. 17). Since salicylates exert an anti-inflammatory effect, part of the pain relief appears to be due to preventing or reducing the inflammation and removal of one of the sources of the stimuli to the pain receptors. However, this viewpoint is not substantiated by the fact that blood-borne phenacetin and acetaminophen are analgesic but lack significant anti-inflammatory properties, while phenylbutazone is an effective anti-inflammatory agent, but possesses feeble analgesic properties. Lim and associates (Ref. 19) noted that salicylates apparently block painful stimulation of visceral receptors caused by intra-arterially or intraperitoneally injected bradykinin. They postulate that the analgesic effect is due to blockage of chemoreceptors mediating pain. Whether the salicylate effect is confined to endothelial and mesothelial structures where bradykinin may be a mediator of pain is still not known. More recent data indicate that salicylates act by preventing the synthesis of prostaglandins, thereby alleviating or preventing local inflammation which is not due to antagonizing the effects of bradykinin (Ref. 9). These concepts relate to the blood-borne drug in the tissues and are not supportive evidence of a direct local action caused by penetration of the aspirin into the mucous membranes. Gastric absorption and not local transfer is mentioned in these studies. Scott (Ref. 20) reported that topical application of aspirin to dentinal receptors in cats inhibits both steady-state discharge and response to a brief heat stimulus. The minority of the Panel notes that these studies were done on dentine and not mucous membranes.

Chewing gum formulations containing aspirin in a gum base have developed supposedly to provide a greater retention and absorption of the drug and to produce a topical local effect on the surrounding tissue. One marketed preparation bears the labeling "for the relief of minor sore throat pain, muscular aches, and pain." Although the labeling does not specifically state that the effect is relief of sore throat due to the topical application of the aspirin, the user of such a product cannot help inferring that this is what is meant. Data in the submission for the product do not adequately support this contention. The minority of the Panel concurs with the sentiments of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products which states as follows in the **Federal Register** July 8, 1977 (42 FR 35376–35377).

Historically, aspirin has been used as a gargle for the treatment of minor sore throat pain. Chewing gum formulations containing aspirin in a gum base were developed to provide for greater retention and absorption of the drug and to produce a topical, local effect on the surrounding tissues. These formulations may also make the medication more pleasant to take. Chewing gums with aspirin are primarily used and labeled for "relief of minor sore throat pain." However, other traditional labeling is also included such as "for headache, muscular aches, and pain." The latter claims can only be attributed to the absorption of the drug into the systemic circulation.

The Panel concludes that aspirin or any analgesic in a gum base, with the specific claims for the relief of sore throat, has not been adequately tested for effectiveness. This use of aspirin may not be desirable or safe particularly if the tissue is highly inflamed or abraded because aspirin is irritating to the mucosal tissue as discussed above. The Panel recommends that claims of aspirin-containing gum for the relief of sore throat or the use of aspirin as a gargle for a local effect properly belongs in a review of ingredients claimed for treatment of sore throat in general and should therefore be deferred to the Advisory Review Panel on OTC Oral Cavity Drug Products for evaulation.

The Panel finds marketing of an OTC analgesic, in a chewing gum formulation, acceptable if the product contains the dosage and Category I labeling claims recommended by the Panel. However, such product formulations containing aspirin should include the warning, "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advise and supervision of a physician." As with chewable tablets discussed above, oral mucosal damage may occur from the use of chewing gum aspirin products and this effect of aspirin on blood clotting may be a factor in such situations.

The minority of the Panel has examined the data in the subjective study conducted by Bernstein and Nelson (Ref. 2). In this study 20 patients with evidence of sore throat and pharyngitis were given aspirin in a gum vehicle and a placebo. Pain was induced by having the subjects chew a cracker and swallow with water. Although the submitted data indicate that the subjects felt less pain after taking the gum containing aspirin and preferred this preparation to the placebo, the minority of the Panel does not feel that the study proves that the pain relief reported was due to a local anesthetic effect on pain receptors in the throat and not from a systemic action of the absorbed aspirin.

The minority of the Panel agrees with the OTC Advisory Review Panel on Internal Analgesic and Antirheumatic Products that aspirin in a gum base with specific claims for relief of sore throat by a topical action has not been adequately studied, and that there is much evidence indicating that it is without appreciable topical analgesic effect and that the effect is probably a systemic one due to the aspirin that is swallowed and absorbed. The topical use of aspirin may not be desirable or safe, particularly if the tissues are highly inflamed or abraded, because aspirin is irritating to the mucosal tissue. The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, in the **Federal Register** of December 4, 1979 (44 FR 69845–69847), has likewise concluded that even though percutaneous absorption of salicylate does occur, its action is systemic when topically applied and not local on the receptors for pain. Some degree of percutaneous absorption of salicylate esters occurs through the intact skin (Refs. 1, 22, and 23), but no significant cutaneous analgesic or anesthetic activity has been demonstrated. Likewise some absorption occurs from the normal mucous membranes. No controlled studies exist demonstrating that the relief of pain is due to topical application. Any analgesic effect that is obtained is due to the systemic effect that follows absorption from the stomach and oral mucous membrane after topical use. Aspirin is the best absorbed of all salicylates percutaneously from aqueous and other solutions. The percutaneous absorption of aspirin is increased 30 percent when 2 percent camphor is present. In a statement attributed to Fantus (Ref. 24), it is said that the absorption of salicylates through the skin is increased if the solution contains 20 percent alcohol. There is no indication that there is any correlation between these findings concerning absorption from the skin and the absorption of asprin from the mucous membranes of the oral cavity. Blood levels of salicylates have been demonstrated after cutaneous application using tracer elements in animals. Excretion of salicylates and metabolites into the urine have been demonstrated after percutaneous absorption and absorption from the mucous membranes. Comparison of blood levels following topical application on the oral and pharyngeal mucous membranes with those following oral ingestion of therapeutic doses have not been made.

One Panel member made an oral presentation on a particular commercial product containing aspirin in chewing gum at the August 14, 1979 meeting of the Advisory Review Panel on OTC Oral Cavity Drug Products (Ref. 25). The Panel member stated that aspirin in chewing gum is effective as a topical analgesic. No written submission was presented to the Panel. The minority of the Panel could not evaluate the data presented in such a manner. The Panel member was told to submit a report for distribution to the Panel and that the data would be analyzed statistically by FDA for validity. No submission was received by FDA or any Panel member for study and evaluation of data submitted from personal experimentation using the "Adriani Method." How the method was used, the type of subjects studied, and other pertinent data were not presented. If they were, they were unclear to the minority of the Panel.

At the final Panel meeting the subject was discussed further and the same Panel member discussed the effectiveness of the same commercial product and presented views which, to the minority of the Panel, appeared to reflect private opinions rather then scientific facts (Ref. 26).

Adriani, Minokadeh, and Naraghi (Ref. 27) have studied the analgesic effects of a saturated solution of aspirin swabbed on the forepart and tip of the tongue using the method of Adriani and Zeppernick. Pain was induced with a direct electric current of a pulsatile type of 20 cycles per second and at a voltage range of 1 to 5 volts. The study was double-blinded and performed on 10 adult healthy volunteers. Saline was used as a control (placebo). Initially, every subject complained of a stinging sensation when the aspirin was applied. This disappeared after several minutes. However, no sensation of numbness developed at any time. The aspirin was not more effective in abolishing the painful stimulus than the placebo. Benzocaine in propylene glycol was swabbed over the same area after completion of the testing. In each case, after the use of placebo and the aspirin, numbness resulted from the use of the benzocaine. A saturated solution of acetaminophen was applied in the same manner as aspirin. No burning sensation was experienced by any subject. Likewise, there was no diminution in response to pain. The response to aspirin was the same as with acetaminophen and the placebo. It is obvious from these data that aspirin possesses no local analgesic or anesthetic activity.

The minority of the Panel concludes from available data that the action of aspirin applied topically is systemic and that any analgesic effect is due to the blood-borne drug that is absorbed. The minority of the Panel finds no data to substantiate claims that blood levels following topical application of aspirin on the skin or mucous membranes are sufficient to produce topical analgesia or anesthesia.

The minority of the Panel accepts the fact that aspirin acts in a dual manner in producing analgesia; one acting centrally in the brain and one acting peripherally by the blood-borne drug acting as an anti-inflammatory agent. It does not support the assumption that is made that the drug penetrates the mucous membranes and exerts its effects topically on the pain receptors and other structures beneath the mucosa or neutralizes such substances as bradykinin or prostaglandins directly by passage through the inflamed mucous membranes.

In the **Federal Register** of July 8, 1977 (42 FR 35375–35376), the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products stated:

> Chewable tablets offer a convenient method of administering the drug to individuals who have difficulty in swallowing whole tablets. This dosage form is especially popular for use in children. There are many marketed children's chewable aspirin tablets, which are usually flavored, containing 80 mg (1.23 gr) of aspirin per dosage unit. These tablets may be chewed, crushed on a spoon, dissolved on the tongue, or even swallowed as a conventional tablet. The Panel finds these chewable, flavored tablets acceptable and recommends that all such tablets containing salicylates for children under 12 years be labeled, "Drink water with each dose." In addition, as noted elsewhere in this document, because aspirin can increase bleeding, the Panel recommends that chewable aspirin-containing tablets be labeled with the warning, "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician."

The minority of the Panel notes that washing with water after chewing the tablets is advised presumably to avoid prolonged contact and aspirin burns.

It is consensus of the minority of the Panel that the topical use of aspirin in any form is unwarranted and unjustified. Reasons for this include the possible injury to the mucosa of the mouth and throat, the paucity of data on effectiveness as a topical analgesic, the possibility of bleeding problems, and because safer and more effective agents are available for relief of pain of sore throat and sore mouth.

(iii) *Proposed dosage.* Adults and children 3 years of age and older: 130 to 500 mg of aspirin per unit, incorporated in a chewing gum base; chew 1 gum tablet every 4 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(iv) *Labeling.* The minority of the Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

In addition, the minority of the Panel recommends the following specific labeling:

*Warnings*—(*a*) "Do not use if you are sensitive or allergic to aspirin."

(*b*) "Do not use if you have bleeding problems."

(*c*) "Do not use without a physician's advice if your mouth or throat is highly irritated, inflamed, or ulcerated."

(*d*) "Do not use if you have stomach ulcers."

(*v*) *Evaluation.* Data to demonstrate effectiveness should be required in accordance with the guidelines set forth below for OTC oral health care anesthetic/analgesic active ingredients. (See part III. paragraph C. below—Data Required for Evaluation.)

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b. *Benzocaine.* The Panel concludes that benzocaine is safe and effective as an OTC anesthetics/analgesics active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzocaine is an effective topical anesthetic/analgesic that has enjoyed widespread and long-term usage. Benzocaine was also called anesthesin, orthocesin, and parathesin. It was official for many years in the "United Stated Pharmacopeia." Benzocaine is also listed in the "National Formulary XIV." Benzocaine is the ethyl ester of aminobenzoic acid. It may be prepared by reducing paranitrobenzoic acid to aminobenzoic acid and esterifying the latter with ethyl alcohol in the presence of sulfuric acid. Benzocaine is a white, crystalline, stable powder which melts at 88 to 92° C. It is odorless and has a somewhat bitter taste. The powder induces a sense of numbness when placed on the tongue.

Benzocaine is one of a group of several anesthetics/analgesics which are often referred to as the "insoluble" topical anesthetics/analgesics. This group includes the propyl ester of aminobenzoic acid (propaesin), the butyl (butamben) and two other chemically related compounds called orthocaine and orthoform new (Ref. 1). The safety of benzocaine is due to the fact that it is poorly soluble in water. One gram benzocaine dissolves in 2,500 mL water, 5 mL alcohol, 2 mL chloroform, and 4 mL ether. Benzocaine is lipophilic and is soluble in various oils, such as olive, peanut, and almond oil. It is also soluble in petrolatum, dipropylene glycol, and various polyethylene glycols. Benzocaine is stable in air. However, if boiled with hydrochloric acid, it is hydrolyzed and converted to aminobenzoic acid and ethyl alcohol. Benzocaine is a base by virtue of the amino group on the benzoic acid nucleus. Because it is lipid soluble and poorly ionized, it readily penetrates the lipid barriers of the cell membranes. Benzocaine forms salts with hydrochloric acid and other acids. The hydrochloride salt is irritating to the mucous membranes and to the skin.

Benzocaine has slight antiseptic and bacteriostatic actions, but these actions are not clinically significant. Benzocaine acts, as do other topical anesthetics, on the axonal membrane to interrupt conduction. As is the case with other local anesthetics, it stabilizes the membrane and prevents passage of sodium ions into the axonal cytoplasm, thereby preventing depolarization. Its anesthetic activity is decreased or lost when formulated in an acid medium because it forms salts by the interaction of acids with the amino group (Refs. 1, 2,

and 3). The salts are ionized and do not readily penetrate the lipid barriers of cell membranes. The buffering mechanisms of mucous membranes act to release the basic form. For this reason, the salts are effective on the mucous membranes but not on the intact skin.

(1) *Safety.* The Panel concludes that benzocaine is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzocaine is one of the most widely used and safest topical anesthetics in OTC preparations. In one year 1,300,000 pounds (lbs) were used in the United States for OTC and prescription use. Because it has a low degree of water solubility, the quantities absorbed are relatively insignificant, and plasma levels that cause systemic reactions characteristic of the soluble "caine" type drugs and their allies do not occur with benzocaine. The convulsions and cardiac depression resulting from high plasma levels of the "caine" type drugs do not occur with benzocaine and reports of such reactions with the use of benzocaine are nonexistent. Blood plasma contains pseudocholinesterases which hydrolyze and detoxify esters of aminobenzoic acid, such as procaine, butethamine, and tetracaine. The exact metabolic pathways for the biodegradation of benzocaine in man is not known (Ref. 1). However, it is likely that benzocaine undergoes hydrolysis into aminobenzoic acid and ehtanol. The aminobenzoic acid is converted to aminohippuric acid, or is conjugated with glycine, or is excrete unchanged into the urine.

Benzocaine has been administered orally to relieve stomach pain without any resulting toxic effects. It causes some discomfort by the oral route probably because it forms the hyrochloric salt which is irritating. The lethal dose in man is not known. The Panel is unaware of any fatalities due to oral ingestion of benzocaine. Lethal doses have been determined in animals when benzocaine has been administered by various routes. Astrom and Persson (Ref. 4) determined the toxicity of benzocaine in rabbits and compared it with that of several other soluble topical anesthetics/analgesics of the "caine" type. The anesthetics/analgesics were applied to various mucous surfaces by the intravesicular, intranasal, and intratracheal routes. When administered by the intratracheal route, the $LD_{50}$ (mean lethal dose) for benzocaine was 146 mg/kg (milligrams per kilogram). For tetracaine, it was 4.4 mg/kg. For cocaine, the $LD_{50}$ was 30 mg/kg, and for lidocaine, it was 75 mg/kg. When the drugs were administered intranasally, the $LD_{50}$ for benzocaine was 104 mg/kg, compared to 10 mg/kg for tetracaine, 50 mg/kg for cocaine and 135 mg/kg for lidocaine. Using tetracaine as a reference unit of toxicity and designating this unit as 1, the toxic dosage relationships would be tetracaine 1, cocaine 6.8, lidocaine 17.1, and benzocaine 33.2 when the drugs were administered by the intratracheal route. In other words, approximately 33 times more benzocaine would be required to cause a fatal response than would be required if tetracaine were used. By the intranasal route, the toxic dose relationship is tetracaine 1, cocaine 5, benzocaine 10.4, and lidocaine 13.5. These comparisons indicate that benzocaine is far less toxic than the other compounds tested when administered via the intratracheal and intranasal routes. The data also indicate that when the intranasal route is used, benzocaine is far less toxic than tetracaine and cocaine but slightly more toxic than lidocaine.

Acute lethal dose studies using the oral and intraperitoneal routes of administration in mice also indicate that benzocaine manifests a low degree of toxicity. Zaroslinski (Ref. 5) studied the effects of benzocaine on the cornea of rabbits to determine its potential for producing irritation. The concentrations used ranged from 4 to 20 percent in polyethylene glycol-4,000 dilaureate. Benzocaine caused no detectable irritation of the eyes. He compared benzocaine with the effects of the hydrochlorides of dibucaine, tetracaine, and pramoxine. Dibucaine hydrochloride, 2 percent, and tetracaine hydrochloride, 2 percent, caused irritation consisting of a red, swollen conjunctival sac with copious mucous secretions surrounding the area. This condition persisted in these animals for 48 hours. Pramoxine hydrochloride, 3 to 4 percent, caused extreme swelling and inflammation at the experimental site. The irritation was accompanied by excessive mucous secretion. After 24 hours, the corneal areas became blue in appearance, suggesting blindness.

The systemic effects of benzocaine absorbed percutaneously were also studied by Zaroslinski (Ref. 6). These studies were designed to assess the effects of benzocaine on the hematopoietic system and were conducted in rabbits (Ref. 5). Benzocaine, 20 percent, in a Carbowax™ base was applied to abraded rabbit skin after which blood samples were drawn from a marginal ear vein. Hemoglobin and methemoglobin levels were determined. In addition, erythrocyte, leukocyte, and differential counts were made. The hemoglobin level decreased to the same approximate levels in both the control and experimental animals. Methemoglobin levels increased to less than 3 percent of the total hemoglobin. This response was essentially identical to that occurring in the control and experimental animals. Erythrocyte levels decreased in both the control and experimental animals while the leukocyte count was elevated in both the test and control animals. Differential counts revealed an increase in polymorphonuclear leukocytes and a decrease in lymphocytes in both the control and experimental groups. It was concluded, even though some minor change occurred in each of the parameters studied, that these changes were indistinguishable in the control and experimental groups and that these effects were apparently due to some phenomena other than that of applying the ointment to the abraded skin.

The percutaneous safety of benzocaine was reported by Zaroslinski (Ref. 5) in a study investigating the local effects of repeated application of benzocaine to the abraded skin. The experiment was designed to establish whether or not the use of benzocaine applied repeatedly to the abraded skin of rabbits caused any irritancy or allergenic responses as well as systemic adverse effects. The study was conducted in eight female albino rabbits weighing 2.2 to 3.4 kg. The back of each animal was closely clipped and then abraded in a specific area by repeatedly scraping the skin with the edges of a piece of wire screen, the teeth of which were 1 mm apart. The rabbits were divided into two groups. One group received 5 g ointment twice daily applied to the abraded surface. The second group served as a control, and no ointment was applied. Blood samples were drawn from the marginal ear vein of each animal before and after abrading and tested for the hemoglobin-methemoglobin content, changes in erythrocytes, leukocyte counts, and differential counts. The areas of the abrasion were varied, i.e., they were 3, 6, and 12 square inches, respectively. In all instances the quantity of ointment applied was constant, i.e., 5 g. The weighed amount of ointment was spread uniformly over the abraded areas. The skin was then manipulated by rubbing to cause absorption of the ointment. The entire trunk of each rabbit was protected by a light, muslin bandage.

The drug was applied twice daily, 5 days weekly over a period of 20 days. During this time 200 g of the ointment was applied to the abraded skin area of each of the rabbits. No observable local irritation or signs of allergic reaction were noted nor were there any demonstrable systemic effects as judged by observations of the hematological parameters. During this period, each test animal was inuncted with approximately 80 g/kg ointment. The variations observed in the hemoglobin and methemoglobin values were similar in both the control and the experimental animals.

Safety data in people are available. Historically, the use of benzocaine preparations for topical anesthesia, both on the skin and mucous membranes, and for use internally has been reported many times and has been associated with a high degree of safety. It is beyond the scope of this Panel to cite in detail the case reports and other references pertaining to the clinical use of benzocaine, both as a prescription drug and in OTC preparations since its introduction in 1903 by Einhorn. Many of these reports appear in the older medical literature and are not readily available, including reports of uncontrolled studies.

The Panel, however, cautions users that benzocaine therapy is not absolutely without hazard. In reviewing the literature on benzocaine, the Panel noted two types of adverse reactions. These reactions are either due to sensitization and are allergic in type or result in methemoglobinemia. The data cited in the medical literature on adverse reactions to benzocaine often focus on isolated cases or a small number of cases documenting adverse reactions. Much of these data are retrospective and cite the use of combinations containing benzocaine as one of the ingredients. It is difficult to extrapolate from the frequency of occurrences of these isolated cases the probability of occurrence of adverse reactions in the general population, since no data were furnished on the frequency of application or the number of subjects treated with the drug.

As is the case with other drugs, benzocaine can act as a hapten and combine with proteins to cause a sensitivity mediated by IgE immune globulin type of antibodies. These antibodies act on mast cells basophils, and other cells in susceptible individuals and cause anaphylaxis (allergic reactions), rhinitis (nasal inflammation), intrinsic asthma, urticaria (hives), and atopic dermatitis. Benzocaine can also activate the thymus-lymphoid system and cause local sensitization of the cytotoxic type in the skin after repeated applications. The mechanism for development of sensitization is described elsewhere in this document. (See part II. paragraph E. above—Adverse Reactions.)

Fisher, Pelzig, and Kanof (Ref. 7) studied the ability of paraphenylenediamine, a hair dye, to act as a sensitizer on the skin to produce an allergic edematous contact type of dermatitis. They found that in a group of 50 high-risk patients, 2 patients had positive patch reactions to paraphenylenediamine and that 18 patients were also found to be sensitive to benzocaine. They also found that of 24 patients sensitive to benzocaine, 10 were also sensitive to paraphenylenediamine. In a similar study, Gaul (Ref. 8) using a patch test found that in a group of 580 dermatologic patients, 50 were sensitive to paraphenylenediamine and 16 were sensitive to benzocaine. Of the benzocaine-sensitive patients, three were sensitive to benzocaine only and three were sensitive to paraphenylenediamine, procaine, and benzocaine. Patients showing sensitivity to a variety of substances were characterized as having "cross-sensitivity," "cross-and multiple-sensitivity," and "multiple-sensitivity without cross-sensitivity." The Panel emphasizes that benzocaine is chemically dissimilar to paraphenylenediamine. Since benzocaine can act as a hapten and combine with a tissue protein to form strong covalent bonds to act as an allergen, these findings are not surprising to the Panel.

In the North American Dermatologic Study (Ref. 9), the incidence of benzocaine irritancy and sensitivity was less than 5 percent and equal with other commonly used drugs and less than the more frequent sensitizers, such as neomycin. These studies were performed on high-risk allergic patients seeking treatment for dermatologic diseases. Benzocaine has often been referred to as a potent sensitizer and has been said to cause sensitization and cross-sensitization to other derivatives of aminobenzoic acid, such as procaine, butamben, butethamine, tetracaine, and related compounds. The number of reported reactions that have occurred has not been correlated with the total number of applications of the agent to individual subjects, with repeated applications, and with subjects who are not high risk (Ref. 10). Cross-sensitivity is defined as the capacity of an antibody to react not only with the antigen responsible for its production but also with other antigens that are closely allied chemically. Mathieu (Ref. 11), in reviewing the liteature on cross-sensitivity, found instances of cross-sensitivity among all the local anesthetics to be rare, irrespective of the mode of the administration.

The Panel concludes that the available epidemiologic data on allergy, irritancy, and other reactions are inconclusive and in no way support the contention that benzocaine is a "potent sensitizer." The number of adverse reactions is relatively small when one considers that benzocaine has been used since the early 1900's and has enjoyed wide marketing experience with few complaints. It has been and still is one of the most widely used and safest topical anesthetics in OTC preparations (Refs. 6, 12, and 13). The Panel also feels that such depictions as "potent sensitizers," "common cross-sensitizers," and "highly allergic," imply that these phenomena occur with greater frequency with benzocaine than with other drugs and that such statements are unwarranted. The Panel finds little or no evidence of controlled, investigative, or epidemiological studies to support these contentions. Calnan et al. (Ref. 14) evaluated sensitivity of various allergens by patch tests in 281 housewives exhibiting hand dermatitis in an effort to identify the offending allergen. Only 5 percent of these patents proved to be sensitive to benzocaine. Substances occurring in household items or in chemicals such as balsms, nickel, and rubber were more common allergens than was benzocaine. Bandmann et al. (Ref. 15) in their reevaluation of some of the same data originally reported by Calnan et al. (Ref. 14) showed that the incidence of positive patch tests with benzocaine in male and female patients with allergic dermatitis was 3.3 percent and 4.5 percent, respectively. In view of the fact that only a fraction of the population exhibits any allergic dermatitis, and in view of the fact that these tests were done on high-risk populations, the Panel is of the opinion that the incidence of benzocaine sensitivity is quite low.

One death due to anaphylactic shock immediately following the administration of throat lozenges containing 10 mg benzocaine, 1 mg tyrothricin, and chlorophyll was reported by Hesch (Ref. 16). Circumstantial evidence cited by the author suggests that the death was drug related. However, it was impossible to state which of the components in the lozenge was the causative agent. The Panel is unaware of any similar cases of

anaphylaxis that could be attributable to benzocaine or benzocaine-containing products and concludes that even though benzocaine can act as a hapten and induce an IgE-mediated anaphylactic response, particularly on damaged skin and mucous membranes, the occurrence of anaphylaxis is extremely rare. The use of a 20-percent benzocaine ointment in 132 patients suffering from 22 types of dermatologic conditions was documented by White and Modura (Ref. 17). Included among these were 10 cases of infantile eczema, both dry and weeping, and 10 cases of varicose ulcers. Of the 132 cases, the relief obtained with benzocaine was inadequate in only 2 cases of atopic dermatitis and in 2 cases of lichen simplex chronicus. There were no cases of irritation or sensitivity reactions directly attributable to benzocaine. However, there were 2 cases of aggravation of dermatitis venenata (poison ivy) but not of the atopic dermatitis. Thus, relief due to benzocaine was adequate to excellent in 126 out of 132 patients. The incidence of side effects was 2 out of 132 patients, and these were not of a serious nature. This type of study in a population selected on the basis of dermatologic disease rather than on the basis of the history of drug allergy, tends to provide a better estimate of the incidence of sensitivity in the general population.

Adriani and Campbell (Ref. 18) in a study of the absorption of tetracaine applied on the mucous membranes in various areas of the body comment that the systemic absorption of benzocaine is poor even though benzocaine was not included in this study. They attribute the absence of untoward reactions in 10,000 patients treated with 20-percent benzocaine ointment as a lubricant anesthetic for deadening of pharyngeal and tracheal reflexes during the introduction of endotracheal tubes to this lack of significant absorption. Adriani and Zepernick (Ref. 19) reported a total lack of adverse reactions in over 144,000 cases in which 20 percent benzocaine was used in hospitalized patients. The majority of these cases involved single applications for the lubrication of endotracheal tubes, oropharyngeal airways, and other instruments used in the pharynx and trachea during clinical anesthesia. The studies were performed at the Charity Hospital, New Orleans. Since that time there has been a continued use of benzocaine for the same purpose, and it is estimated that the number of usages since their report was published is an additional 200,000, all without any adverse or allergic reaction.

Prystowsky et al. (Ref. 20) did a perspective contact sensitivity study on 1,158 adult volunteers. A pretest history of previous exposure to four allergens, including 5-percent benzocaine in petrolatum, was obtained before patch testing. The patch was removed at 48 hours and read at 5 days. The prevalance of positive reactions to 5-percent benzocaine was 0.17 percent. By history, 85 percent of the volunteers had been exposed to benzocaine. The investigators point out that the 0.17-percent positive reactions to benzocaine in a study of 127 patients referred to clinics for the evaluation of contact dermatitis. They concluded that "the results of this study indicate that contact dermatitis patient populations provide exaggerated estimates of the prevalence of sensitivity to contactants; figures in a general population are preferable in decisionmaking concerning the safety of commercial products."

Methemoglobinemia has been reported following the topical application of benzocaine on both the skin and the mucous membranes. However, this is an uncommon occurrence. It has been reported to have occurred in subjects less than 1 year of age more often than in adults, but it can occur at any age (Ref. 3). Isolated reports of cases of methemoglobinemia, generally in infants following the use of benzocaine-containing products, have appeared in the literature since 1949. Haggerty (Ref. 21) reported a case of a 1-month-old infant who became cyanotic after a weeping diaper rash was treated with an ointment containing 3 percent benzocaine, 1 percent methapyrilene hydrochloride, calamine, zinc oxide, and camphor. The diagnosis of methemoglobinemia was made by spectroscopic examination of the blood. The condition was reversed with methylene blue. Goluboff and MacFadyen (Ref. 22) reported a case of methemoglobinemia in a 3-month-old patient treated for severe eczema and pruritus with several products. One of these products contained salicylic acid, colloidal sulfur, and coal tar; another product contained 1 percent hydrocortisone in an ointment base; and one product contained 1.5 percent crude coal tar, 7.5 percent titanium dioxide, 7.5 percent zinc oxide, 2.5 percent calamine, 1 percent cetyltrimethyl ammonium bromide, and 5 percent benzocaine in a special water-soluble base. In addition the patient received intramuscular terramycin and oral elixir of phenobarbital. Treatment with methylene blue successfully reversed the methemoglobinemia. Determination of the causative agent was impossible due to the multiplicity of ingredients in the preparation.

Other isolated cases of a similar nature have been reported, but the Panel feels little would be added to understanding the nature of this reaction if these cases were reported in detail. Although most reported cases of methemoglobinemia following topical use of benzocaine have occurred in infants, cases have also been reported involving older children and adults. Bloch (Ref. 23) reported a case in a 6-year-old child, and Bernstein (Ref. 24) reported three cases in adults. Hughes (Ref. 25) suggested that the susceptibility might be due to a deficiency of DPNH-dependent methemoglobin reductase, resulting in a diminished capacity to physiologically protect against methemoglobin-inducing foreign compounds. The experiences recorded by Bloch (Ref. 23) in a 6-year-old child suggest that a far less severe methemoglobinemia occurs in older children than in infants. The reactions in the three adults reported by Bernstein (Ref. 21) suggest that the reactions were of a mild nature. He found that definitive therapy was unnecessary. The reductase in the red blood cells converts the iron in methemoglobin (ferrihemoglobin) from the ferric to the ferrous state. The reconversion of methemoglobin to reduced hemoglobin that is constantly occurring does not take place and an accumulation of methemoglobin results when the enzyme is inhibited by the presence of certain drugs. The methemoglobin imparts a bluish color (cyanosis) to the skin of white and lightly pigmented individuals. In Black and heavily pigmented subjects, the cyanosis can be detected in the nailbeds or in the mucous membranes. The rapidity of development of the bluish color depends upon the rate and amount of benzocaine absorbed. In some cases, it develops within 30 minutes to 1 hour after application. Methemoglobinemia due to benzocaine is not life-threatening because only small amounts are absorbed, particularly after a single application of benzocaine. The cyanosis appears when 2 g or more of hemoglobin have been converted to methemoglobin which is incapable of carrying oxygen. In most cases of methemoglobinemia, the oxygen capacity is not signifcantly decreased. Infants under 1 year of age who have not as yet developed sufficient quantities of the reductase allegedly develop methemoglobinemia more easily than older children and adults, but this point has not actually been verified and clarified in the medical literature. On rare occasions,

older children or adults are found who have a congenital deficiency of the enzyme.

Steinberg and Zepernick (Ref. 26) reported a case of methemoglobinemia during anesthesia which occurred in a 38-month-old Black male at Charity Hospital in New Orleans. The child had been anesthetized with cyclopropane on two previous occasions. On the first occasion, anesthesia was uneventful. On the second occasion, induction of anesthesia was followed by the development of cyanosis which was detected by observing the nailbeds. Anesthesia was discontinued; the operation was deferred until a week later. On the third occasion, anestheis was inducted in the usual manner with cyclopropane and the patient intubated. Cyanosis developed within 15 minutes and anesthesia was discontinued. He remained cyanotic even though he was awake and receiving 100 percent oxygen. There was no change in pulse or blood pressure. Within 4 hours, he regained his normal color and had no apparent ill effects from the experience. A review of the anesthetic records revealed that anesthesia in the first instance, when anesthesia was uneventful, was conducted by using an endotracheal tube that had been lubricated with petrolatum. On the second and third occasions, the endotracheal tube had been lubricated with an ointment containing 20 percent benzocaine in propylene glycol.

The child was studied further by Adriani and Zepernick (Ref. 27). Reapplication of 20 percent benzocaine to the mucous membranes of the mouth and on the tongue promptly produced cyanosis without respiratory distress and without changes in pulse and blood pressure which one would anticipate had suboxygenation been the causative factor. Blood drawn at this time was the color of chocolate. When analyzed spectroscopically, the absorption spectrum was characteristic of that produced by methemoglobin. The cyanosis cleared promptly following the intravenous administration of 1 mg/kg methylene blue in a 1-percent solution. On subsequent days, various drugs were applied to the mucous membranes and the blood analyzed for methemoglobin. Since benzocaine is chemically allied to procaine, the latter being the diethylaminoethanol ester of aminobenzoic acid, procaine was applied to the mucous membranes and the blood analyzed for the presence of methemoglobin. None was found. A saturated aqueous solution of aminobenzoic acid was likewise applied on the mucous membranes with no resultant cyanosis or evidence of methemoglobinemia. A paste consisting of propylene glycol and butamben was likewise applied without any development of methemoglobinemia. Since ethyl alcohol is used to esterify aminobenzoic acid to form benzocaine, it also was applied to determine whether or not there was cross-sensitization with the components of benzocaine. Alcohol, also, did not produce cyanosis nor did the blood show any increase in methemoglobin. The results following the use of 1 percent lidocaine hydrochloride on the mucous membranes were also negative. Propylene glycol applied to the mucous membranes also caused no methemoglobinemia. It appears obvious from these studies that the formation of the methemoglobin was due to the ethyl ester alone and that there was no cross-reactivity between aminobenzoic acid or any of its derivatives.

The majority of the reports that the Panel has reviewed concerning the formation of methemoglobinemia following the use of benzocaine are single, isolated cases of one, two, or three occurrences. It is difficult to extrapolate from these isolated cases with what incidence methemoglobinemia might occur in the general population since the occurrences have not been in any was correlated with the total number of drug applications. Adriani and Zepernick (Ref. 19) reported no cases of sensitivity nor any other adverse reactions in over 144,000 cases after the use of a preparation containing 20 percent benzocaine for lubrication of endotracheal tubes and airways in hospitalized patients. Of these 144,000 cases, there was only 1 occurrence of methemoglobinemia following the application of the benzocaine ointment as a lubricant (Ref. 27).

Methemoglobinemia is not life threatening, particularly when caused by the small amounts of benzocaine absorbed percutaneously or from the mucous membranes following a single application. Methemoglobin is also known as ferrihemoglobin and is incapable of carrying oxygen since the iron has been converted from the ferrous to the ferric state. Cyanosis becomes apparent when 10 to 15 percent of the total hemoglobin has been converted. Methemoglobinemia becomes symptomatic when 30 to 45 percent methemoglobin levels are attained if acutely induced. The symptoms are fatigue, dyspnea, weakness, tachycardia, and headache, and are due to hypoxia produced by the lowered oxygen capacity of the blood. Normally, there is an equilibrium between the concentration of ferrous and ferric components of iron in the hemoglobin. Normally, not more than 1 percent of the iron is in the ferric state. When iron is converted to the reduced state, it can carry oxygen if the globin is not altered. If the globin is altered, cathemoglobin forms. Cathemoglobin is incapable of carrying oxygen even though the iron is reduced to the ferrous state.

There are at least three recognized enzymatic processes which tend to keep the heme moiety of hemoglobin in the ferrous state and reduce the iron to the ferric state as rapidly as the ferrihemoglobin forms. The first mechanism employs an electron donor, nicotinamide adenine dinucleotide ($NAHDH_2$), which is formed from the oxidation of glucose and reduces the ferric heme to the ferrous state in the presence of the enzyme metheglobin reductase. This pathway is the most important of the three and accounts for 67 percent of the conversion of the ferric iron to the ferrous state in red blood cells.

The second pathway by which reduction of methemoglobin is accomplished involves the generation of nicotinamide adenine dinucleotide phosphate ($NADPH_2$) formed in a pentose pathway. In this reaction, methemoglobin can act as a cofactor that facilitates and accelerates the reaction. This pathway accounts for only 55 percent of the reduction of the iron in the red blood cells from the ferric to the ferrous state. The third mechanism involves a glutathione pathway. $NADPH_2$ in the presence of glutathione reductase (GR) reduces the oxidized glutathione to reduced glutathione. The reduced glutathione in the presence of glutathione peroxidase is capable of destroying oxidant compounds capable of oxidizing hemoglobin. This pathway accounts for 12 percent of the methemoglobin converted to normal hemoglobin. Ascorbic acid is a reducing agent and can also be involved in the conversion. It reduces 16 percent of the methemoglobin; however, this is a nonenzymatic process.

The etiologic factors which alter equilibrium between ferrous and ferric iron can be classed into primary and secondary factors. Primary factors are hereditary. In the hereditary states, methemoglobinemia is due to a deficiency of $NAHDA_2$-dependent methemoglobin reductase and hereditary methemoglobinemia with an abnormal hemoglobin. These conditions are rare. The secondary factors are oxidant drugs.

Concentrations of methemoglobin not exceeding 8 percent of the total hemoglobin are normally present without cyanosis. Cyanosis, as stated above, becomes apparent when the methemoglobin level exceeds 10 to 15 percent of the total circulating hemoglobin; however, levels up to 30 percent of the total hemoglobin may produce cyanosis, but not necessarily any clinical symptoms. Methemoglobinemia becomes symptomatic when 30 to 45 percent of the total hemoglobin is oxidized to methemoglobin.

Recently, Rao, Naraghi, and Adriani (Ref. 28) studied the blood levels of methemoglobin following the instillation of 1 g benzocaine in propylene glycol in the mouth of infants under 6 months of age and in adults. The methemoglobin levels in the controls ranged from 0.1 to 3.5 percent expressed in terms if diminution in oxygen-carrying capacity of the total hemoglobin in the controls. In infants there was an increase in the degree of unsaturation during the first hour to an average of 4.5. This is not as striking as one would anticipate. There was a gradual decrease in the methemoglobin content during the second hour, but it did not return to the pretreatment level in any subject until after the third hour. Surprisingly, the mean level in adults was higher than that found in infants. This is a direct opposition to what has been postulated concerning the ease of development of methemoglobinemia in infants following the use of the drug. The Panel concludes that the occurrence of methemoglobinemia following the use of benzocaine is rare. Normal infants and children are not more prone to its development than adults. Why this simple nonoxidizing chemical compound should cause this response on rare occasions is not known, but the Panel concludes it can be classified as an uncommon idiosyncratic response that is in no way injurious or life threatening.

Benzocaine differs from the drugs and chemicals, such as acetanilia, sulfanilamide, the aniline dyes, and the nitrites. These latter drugs and chemicals cause methemoglobin to form at a more rapid rate than can be reduced by the enzyme, even though the enzyme is present in adequate quantities in the red cell.

(2) *Effectiveness.* The Panel concludes that benzocaine is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzocaine is an effective topical anesthetic/analgesic on the skin and mucous membranes. There are many reports in the medical literature of its long, continued, successful use as an anesthetic and an antipruritic in the form of ointments, lotions, sprays, lozenges, and dusting powders that attest to its effectiveness (Refs. 3, 12, 19, and 29). These studies, however, are subjective and uncontrolled. Benzocaine is not suitable for infiltration or perineural injection. When properly formulated with ingredients that insure its stability and continuous contact with a cutaneous or mucous surface it provides prolonged anesthesia (Ref. 12). When incorporated in a medium that is sufficiently alkaline to release bioactive quantities of the free base it penetrates both the intact and damaged skin (Ref. 12). Percutaneous absorption and absorption from the mucous membranes occur, but the resulting blood levels are insignificant. Its pain-relieving action is entirely within the skin or mucous membranes. The quantity circulating in the blood is insufficient to provide anesthesia to parts of the body distant from the site of application.

Since the introduction of newer and more suitable solvents, such as the glycols, there has been a renewed interest in the use of benzocaine as a topical anesthetic/analgesic because of greater effectiveness of preparations formulated with these solvents compared to the oleaginous basis and dusting powders used heretofore. The concentration of benzocaine in the tissue fluids that is bioactive is insufficient to penetrate large nerve trunks. The effect of benzocaine is entirely at the terminal pain receptors in the mucous membranes.

Benzocaine is an effective topical anesthetic/analgesic on the mucous membranes. It as a short latent period on the mucous membranes of the mouth ranging from 30 seconds to 1 minute. The duration of action varies with the duration of contact. A single application of a solution that is diluted with saliva in the mouth and washed away produces anesthesia of 5 or 10 minutes duration. Continuous contact of a benzocaine-containing preparation will produce anesthetic/analgesic for as long as the drug is present in sufficient concentration at the particular test site. The minimum effective concentration to produce anesthetic/analgesic associated with numbness is 5 percent in propylene glycol. There is little to be gained in exceeding a 20-percent concentration. Adriani and Zepernick (Ref. 19) studied the effects of 40 topical anesthetics used the mucous membranes. They found that although benzocaine was effective it ranked low on the list as far as duration of action is concerned. The most effective drugs were tetracaine, cocaine, lidocaine, dyclonine, and dibucaine. These ingredients, however, are readily absorbed and are capable of producing systemic toxicity.

Benzocaine is safe because of its low water solubility; even though concentrations of 20 percent may be applied in a solvent, such as propylene glycol, the amount that dissolves in the tissue fluids remains the same. The solvent merely increases the concentration so that saturated solutions can be made which are bioactive and will pass into the nerve cells. Concentrations less than 5 percent produce the partial blockade which the Panel has termed "analgesia." Various preparations are available in the form of lozenges and rinses containing benzocaine in concentrations less than 5 percent. These are claimed to be effective for the relief of minor pain in the mouth and in the throat, and to provide temporary relief for a sore throat, ulcer pains, and other afflictions of the oral and pharyngeal mucous membranes. Topical anesthetics/analgesics do not penetrate into the deepest or submucosal structures of the mucous membranes and produce anesthesia/analgesia. They are only effective for surface anesthesia/analgesia.

Preparations designed to relieve sore throat generally consist of sugar-containing lozenges having concentrations of benzocaine from 0.1 to 5 percent. The benzocaine is slowly released and coats the mucosa providing partial anesthesia and temporary relief for sore mouth and throat. The recommended dose under these circumstances does not produce numbness and complete loss of reflex activity. There are those who feel that such a degree of pain relief as would be obtained by using concentrations that produce numbness would interfere with the gag reflex and favor the aspiration of mucus or other material which would be swallowed. On the other hand, it is well known that subjects without gag reflex have no difficult in swallowing. The act of swallowing is not interfered with by cocainization of the pharynx as Doty and Bosma (Ref. 30) were able to demonstrate. Loch et al. (Ref. 31) have confirmed these findings. Freystadtl and Morelli (Ref. 32) have shown that the sensation of touch is still preserved after the sensation of pain has been abolished, which explains the lack of problems. The Panel is unaware of any such accidents occurring with concentrations used in OTC preparations. Benzocaine used in the mouth is swallowed but causes no

systemic toxicity. It has been shown that it is safe in concentrations in solutions of glycols up to 20 percent when applied to oral and pharyngeal mucous membranes. Systemic aborption is so slight that blood levels are barely detectable. Furthermore, blood levels are insufficient to produce adverse reactions such as convulsions or cardiac depression, characteristic of the more soluble local anesthetics. It is the consensus of the Panel that 0.1 to 5 percent concentrations may be used for anesthesia in the form of rinses. Two to 15 mg may be incorporated in lozenges that allow the slow release of the product and continuous bathing of the affected area with a dilute concentration of the benzocaine. The action from sprays, rinses, and gargles is relatively short, since the duration of contact is not early so long as it would be from the slow release from a lozenge. Pain due to ulcers, inflammation of the mucous membranes, etc., may be relieved by using sprays and rinses or swabbing the affected area. The relief is of short duration, usually less than 30 minutes, but in some individuals it may persist for a longer time.

Benzocaine does not penetrate the mucous membranes of the gingiva to relieve pain in the gingiva, tooth, or other types of pain arising in submucosal structures. Benzocaine does not penetrate the mucous membranes into the muscles of the pharynx, tongue, and other structures of the oral cavity. The Panel, therefore, recommends that the labeling for benzocaine-containing products for use in the oral cavity be limited to claims for the relief of soreness or irritation or minor pains of the mucous membranes of the mouth and throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 5.0- to 20.0-percent concentration of benzocaine in the form of a gel or spray not more than three to four times daily. Use a 0.05- to 0.1-percent concentration of benzocaine in the form of a lozenge (equivalent to 2.0 to 15.0 mg per lozenge) every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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c. *Benzyl alcohol.* The Panel concludes that benzyl alcohol is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzyl alcohol is one of the alcoholic or hydroxy-type of topical anesthetics. Benzyl alcohol is phenyl methanol. It may also be looked upon as methyl alcohol with a phenyl group replacing one of its hydrogen atoms. It is also known as phenmethylol hydroxy toluene. It is found in nature in a free state in oil of jasmine (6 percent) and in the form of esters in Peru balsam, tolu balsam, and storax. The commercial product is synthetic, made by

hydrolyzing benzyl chloride or by reducing benzaldehyde. Benzyl alcohol is a colorless liquid with a faint aromatic odor. It has a sharp burning taste and boils at 206° C. It has a specific gravity of 1.042 to 1.047. One gram dissolves in approximately 30 g water making a solution of approximately 4 percent concentration. Aqueous solutions are neutral. Solutions may be sterilized by boiling. Benzyl alcohol is soluble in alcohol (1 g dissolves in 1.5 mL alcohol) and is soluble in ether and chloroform. It dissolves in vegetable oils. Oxidation converts it to benzaldehyde. Slow oxidation occurs if it is exposed to the air for days or weeks. It is stable in stoppered containers (Refs 1 and 2).

(1) *Safety.* The Panel concludes that benzyl alcohol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzyl alcohol is relatively nontoxic. It has been used orally as an antispasmodic agent and rectally as a topical anesthetic/analgesic. It has been used rectally in combination with paraldehyde to anesthetize the mucosa and prevent expulsion of the drug. Benzyl alcohol is converted to hippuric acid in the body and this metabolite is excreted into the urine (Ref. 3).

The effect of large doses of benzyl alcohol was studied in animals by Macht (Ref. 4). The minimum lethal dose of pure benzyl alcohol in white mice is 1 mL/kg. The minimum lethal dose in rats ranged from 1 to 3 mL/kg. In dogs, 2 mL/kg of benzyl alcohol injected intravenously, peritoneally, subcutaneously, and intramuscularly was never fatal. Convulsions and caridiac depression, characteristic of the "caine" type of topical anesthetics, have not occurred when therapeutic or toxic doses of benzyl alcohol have been administered to man or animals. Lethal doses in mice cause respiratory failure and in some cases convulsions. Larger animals, such as dogs, do not manifest these responses. Although benzyl alcohol can, like any other drug, act as a hapten and be antigenic, cases of sensitization have not come to the Panel's attention. The potential for sensitization is lower than it is with the "caine" type of topical anesthetics (Ref. 5).

(2) *Effectiveness.* The Panel concludes that benzyl alcohol is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzyl alcohol belongs to the hydroxy group of topical anesthetics and differs in chemical behavior from the "caine" type drugs. Benzyl alcohol is lipophilic and penetrates the cells of the mucosa and the axonal membranes of nerve fibers. Aqueous solutions of benzyl alcohol are neutral. It does not form salts. Benzyl alcohol is not ionized, and its penetration into the skin and mucous membranes and pharmacologic activity do not depend upon pH. It blocks transmissions of electrical impulses along sensory and motor nerves. Its mode of action is believed to be similar to the "caine" type of drugs.

Macht (Ref. 4) studied the topical anesthetic effects of benzyl alcohol. He obtained anesthesia/analgesia by applying aqueous solutions to the mucous membranes of the mouth, tongue, gums, and lips of patients. The pure alcohol produces a stinging effect when first applied to the tongue followed by a sensation of numbness which may last as long as 2 hours. Macht (Ref. 4) was able to obtain anesthesia/analgesia of the skin by direct application of the pure alcohol. Aqueous solutions of 1 percent produce corneal anesthesia/analgesia in rabbits. Solutions of benzyl alcohol produce sensory and motor blockade when applied to isolated nerves of frogs. Macht (Ref. 4) obtained both motor and sensory blockade by applying 1 percent solutions of benzyl alcohol to isolated sciatic nerves of dogs. Benzyl alcohol in a 1-percent strength has been used for infiltration and perineural block. Stronger solutions are locally irritating and may cause tissue damage if injected parenterally.

Benzyl alcohol manifests varying degrees of bacteriostatic and antiseptic activity. However, this antimicrobial effect does not apply to all pathogenic bacteria and reliance cannot be placed upon it. Benzyl alcohol is effective topically in relieving pain and other discomfort due to ulcers, sore throats, and other lesions affecting mucous membranes of the oral cavity. Solutions composed of equal parts of 33 percent benzyl alcohol, water, and ethyl alcohol are effective in relieving itching and burning on the skin (Ref. 2). Ointments consisting of 10 percent banzyl alcohol in large doses have been used for topical application to the skin.

The duration of action of benzyl alcohol in the usual therapeutic doses is brief depending upon the area of application and duration of contact. The latent period on the mucous membranes is approximately 2 minutes. The duration of action of a 1-percent solution on the skin is usually less than 30 minutes. The duration of anesthetic/analgesic action on the mucous membranes is variable, usually depending upon formulation used. The effect is sustained if incorporated in lozenges and lasts as long as the mucous membranes are bathed in sufficient concentrations. The duration of action when the drug is incorporated in rinses is brief, seldom more than 5 or 10 minutes.

The pure alcohol causes smarting and burning initially when applied to the mucous membranes. Although benzyl alcohol is effective as a topical anesthetic/analgesic, Adriani and Zepernick (Ref. 6) found its effectiveness to be less than that of the "caine" type drugs. However, the Panel concludes that benzyl alcohol is safe and effective for use in drops, rinses, mouthwashes, sprays, or in lozenges on the intact mucous membranes of the mouth and throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 0.05- to 10.0-percent concentration of benzyl alcohol in the form of rinses, mouthwashes, drops, or sprays not more than three to four times daily. Use a 0.05- to 10.0-percent concentration of benzyl alcohol in the form of a lozenge (equivalent to 100 to 500 mg per lozenge) every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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d. *Dyclonine hydrochloride.* The Panel concludes that dyclonine hydrochloride is safe and effective as an OTC

anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Dyclonine is a base which forms a hydrochloride salt. The structure of dyclonine hydrochloride is a modification of the general structural configuration of the commonly used local anesthetics of the "caine" type of drugs, such as lidocaine and tetracaine (Ref. 1). It is a nitrogenous base; however, it is a propiophenone derivative (Ref. 2). One end of the dimethylene chain of the ketone is attached to the nitrogen atom of the piperidine group of the first carbon atom which carries the ketonic group. This is attached directly to a benzene ring which is attached to a butoxy group in the para position. Thus, unlike procaine, lidocaine and other "caine" type drugs, it is neither an amide nor an ester, nor can it be considered an ether, as is the case with pramoxine.

Dyclonine hydrochloride is a white crystalline powder. One gram dissolves in approxiamtely 50 mL water. It is soluble in acetone, alcohol, and chloroform. The crystals melt between 173° and 178° C. It is also soluble in washable cream bases. Its chemical name is 4-n-butoxy-beta piperidino-propiophenone hydrochloride (Refs. 3 and 4).

(1) *Safety.* The Panel concludes that dyclonine hydrochloride is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Although dyclonine hydrochloride is a nitrogenous base, its chemical structure is a departure from that of the "caine" type drugs (Refs. 2 and 3). For this reason, acute systemic toxicity, characterized by convulsions, myocardial depression, hypotension, etc., which are characteristic of the so-called "caine" type of drugs, does not occur.

The acute $LD_{50}$ for dyclonine hydrochloride was studied by Abreu and associates (Ref. 5) in dogs and albino rats. In rats, the intraperitoneal $LD_{50}$ was approximately 45.8 mg/kg; in dogs, the $LD_{50}$ was approximately 9.5 mg/kg. Abreu et al. (Ref. 5) noted that in anesthetized dogs, intravenous doses of 2 mg/kg did not significantly affect blood pressure or pulse, nor did it reduce the cardiovascular response to acetylcholine, or increase the response to epinephrine as demonstrated by a lack of parasympatholytic activity. Doses of 5 mg/kg in anesthetized dogs may cause respiratory failure, but this is reversible, and the animals recover if artificial respiration is instituted.

The cardiovascular effects of dyclonine hydrochloride were investigated in dogs anesthetized with sodium barbital (Ref. 6). The drug was administered over a 25-second period within a dose range of 0.25 to 10 mg/kg in 10 dogs. Dyclonine hydrochloride lowered arterial pressure approximately 10 mm Hg (10 millimeters mercury) at a dose of 1 mg/kg. There was a progressive increase in response at doses of 1, 2, 3, 4, and 5 mg/kg with death being produced at a dose of 10 mg/kg. The mechanism of this reduction in blood pressure was found to be due to a decrease in cardiac output as well as to peripheral arterial dilation. Initially, dyclonine hydrochloride induces some respiratory stimulation when administered intravenously to dogs. As the dosage is increased, depression of respiration and oxygen consumption occurs. Dyclonine hydrochloride has been shown to act as an anticonvulsant, acting as a multisynaptic and spinal reflex depressant (Ref. 6).

Chronic toxicity studies were done with dyclonine hydrochloride in the albino rat and in the dog (Ref. 6). Dyclonine hydrochloride did not significantly affect the growth rate of male or female weaning albino rats as compared to controls when it was administered intraperitoneally for 30 consecutive days. A group of 48 rats were studied. They were divided into four groups. Half of the females and half of the males were given the drug and the other half of each were used as controls. Half of the animals were sacrificed and autopsied. No gross pathologic changes were noted in either group. The drug-treated survivors and controls were mated, and the drug-treated group did not differ from the controls in their reproductive capacity. Upon weaning, the offspring of the first group when subjected to the same experiment also did not differ from their controls either as to growth rate or reproductive capacity. No gross pathologic changes were observed in these animals when sacrificed. Experimental observations in dogs, likewise, showed no gross pathologic changes when given doses varying from 5 to 12 mg/kg twice daily, intramuscularly or subcutaneously. No significant changes from normal were noted in hemoglobin concentration, red and white blood cell counts, and differential counts measured at biweekly intervals (Ref. 6).

In human beings, dyclonine hydrochloride possesses a relatively low degree of toxicity. When applied topically to the skin of 3,656 patients in the form of a cream and to 2,000 additional cases in the form of a solution for topical anesthesia, only two cases of proven sensitivity were reported. It was concluded from these studies that the sensitizing potential of dyclonine hydrochloride under conditions of clinical use is low. In a study using a dyclonine hydrochloride solution, no adverse effects were found. Use of concentrated solutions of 2 percent or more have produced irritations and slough of the nasal mucosa in several cases.

In study dealing with the safety of dyclonine hydrochloride following oral administration, 35 patients were given from 300 to 600 mg daily for periods of time varying from 1 to 12 weeks (Ref. 7). No undesirable side effects occurred. It was concluded that the compound would be entirely safe for human consumption. Adriani and Campbell (Ref. 8) emphasized that the two safest anesthetics for use on the mucous membranes for endoscopic procedures are benzocaine and dyclonine hydrochloride. Each shows the least incidence of systemic reactions.

(2) *Effectiveness.* The Panel concludes that dyclonine hydrochloride is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Dyclonine hydrochloride is a highly effective anesthetic/analgesic for topical use, particularly on mucous surfaces and on abraded and damaged skin. While it is also an effective nerve-blocking agent, it is irritating if injected and may produce sloughing of tissue. It is, therefore, recommended for topical use only. Dyclonine hydrochloride blocks transmission at nerve endings in the same manner as do other topical anesthetics of the "caine" type of closely related to the "caine" type. The product is marketed as a salt (hydrochloride). Dyclonine hydrochloride is not absorbed through the intact skin in significant quantities to produce anesthesia. It is effective on the mucous membranes. In studies on the mucous membranes conducted by Adriani et al. (Ref. 9), dyclonine hydrochloride ranked fourth in effectiveness, being preceded by dibucaine, cocaine, and tetracaine. One percent dyclonine hydrochloride produced a duration of action of anesthesia of 27 minutes, preceded by a latent period of 2 to 3 minutes. The fact that dyclonine hydrochloride is effective on the mucous membranes is well established. The duration of action of dyclonine hydrochloride as an anesthetic/analgesic is considerably

longer than that of benzocaine, benzyl alcohol, and the phenol type compounds. When used in the form of a rinse or gargle, it may relieve pain in irritated mucous membranes for as long as an hour. When incorporated in lozenges that are slowly sucked, the mucous membranes are bathed continously, and it may relieve pain due to sore throat or sore mouth for several hours or as long as an effective concentration is being supplied by the lozenge.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 0.05- to 0.10-percent concentration of dyclonine hydrochloride in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a 0.05- to 0.10-percent concentration of dyclonine hydrochloride in the form of a lozenge (equivalent to 1.0 to 3.0 mg per lozenge) every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice or supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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e. *Hexylresorcinol.* The Panel concludes that hexylresorcinol is safe and effective as an OTC anesthetics/analgesics active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Hexylresorcinol, an aromatic alcohol, is a dihydroxybenzene with a normal hexyl group on position 4 and hydroxyl groups on positions 1 and 3 of the aromatic nucleus. It can, therefore, be classified as a phenol. It responds to certain specific chemical tests characteristic of phenols. Hexylresorcinol is prepared by condensing resorcinol with caproic acid in the presence of zinc chloride. The resulting intermediate product is reduced to hexylresorcinol (Refs. 1, 2, and 3).

Hexylresorcinol is a white or yellowish-white powder composed of needle-shaped crystals. It has a faint "fatty" odor and a sharp astringent taste. It produces a sensation of numbness when placed on the tongue. Hexylresorcinol melts between 62° and 67° C. It turns from a white to a brownish-pink tint on exposure to light and air due to oxidation to quinones. One gram of hexylresorcinol dissolves in approximately 2,000 mL of water. It is freely soluble in alcohol, glycerine, ether, chloroform, benzene, and vegetable oils. For many years, hexylresorcinol was considered official and was included in the "United States Pharmacopeia."

Animal studies indicate a low degree of acute and chronic toxicity (Ref. 4). In rats, the oral minimum lethal dose of a suspension is 50 mg/kg. A suspension in 5 percent olive oil solution administered subcutaneously resulted in a minimum lethal dose of 750 to 1,000 mg/kg. A similarly low degree of toxicity was found in guinea pigs, rabbits, cats, and dogs. In dogs, doses of 1 to 3 g produced no signs of toxicity. When the dogs were sacrificed, mild irritation of the stomach was noted 4 to 5 hours after ingestion of the drug. Lesions in the mucosa were superficial. If the animals were sacrificed 48 hours later, the lesions were not present. Oral administration in rats was well tolerated, revealing no signs of toxicity when 12 mg/kg was repeated six times over a 8-hour period (Ref. 4).

Pure hexylresorcinol is irritating to the respiratory tract and to the skin. A concentration of hexylresorcinol in alcohol has vesicant properties. Hexylresorcinol lacks the irritancy and caustic properties of resorcinol and phenol. Long use over 40 years and extensive marketing experience indicate that hexylresorcinol possesses a low degree of sensitization.

(1) *Safety.* The Panel concludes that hexylresorcinol is safe as an OTC anesthetics/analgesics active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

In view of the fact that hexylresorcinol was extensively used as an anthelminthic and administered orally in both adults and children, the Panel considers hexylresorcinol to be safe for topical application to the mucous membranes and skin (Ref. 5). The usual adult dose as an anthelmintic is 1 g as a single dose in a 24-hour period. For children, the usual dose is 0.1 g for each year of age up to 10 years. The drug is usually given orally after an overnight fast. The presence of food lessens the effectiveness of the drug. A saline purge is usually given the following morning to clear the bowel of dead worms. Treatment may be repeated after 3 days (Ref. 1). Hexylresorcinol has also been shown to have some antimicrobial effects. The drug has been used as a gargle and as a urinary antiseptic. Experiments by Leonard (Ref. 6) resulted in the use of hexylresorcinol as a urinary antiseptic. He found that hexylresorcinol at pH 6 to 6.4 in a 1:60,000 concentration killed microbes in the urine in 1 hour, and that at pH 7.6 to 8.2 a concentration of 1:18,000 was required for the same effect. Robbins (Ref. 7) observed that after oral administration of hexylresorcinol in humans, 18 percent was eliminated in the urine in a conjugated form, and 64 percent was eliminated in the feces in an uncombined state.

(2) *Effectiveness.* The Panel concludes that hexylresorcinol is effective as an OTC active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Hexylresorcinol is a phenol. The substitution of an aliphatic radical on the side chain of this phenol reduces the caustic activity of phenol, but retains the anesthetic qualities of phenol. Thus, the Panel is of the opinion that hexylresorcinol does have anesthetic properties.

Hexylresorcinol solution, 0.1 percent, produces topical anesthesia in the cornea of rabbits lasting up to 10 minutes or more, depending on the concentration of the hexylresorcinol. Hexylresorcinol has been incorporated in lozenges for the relief of sore throat and other painful ailments of the oral cavity.

Adriani and DiLeo (Ref. 8) found that after stimulation by an electric current the application of a commercial preparation consisting of a 1:1,000 solution of hexylresorcinol produced anesthesia on the gums and at the tip of the tongue, but did not completely abolish sensation. The duration of action of aqueous solutions used as rinses, mouthwashes, and gargles is usually short and seldom lasts more than 5 or 10 minutes. When incorporated in lozenges that slowly release the ingredients, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve the pain of sore mouth or sore throat.

The ingredient has also been recommended as an antimicrobial agent for cuts, wounds, and burns on the skin, but the submissions to the Panel do not make this claim (Refs. 9, 10, and 11). The Panel concludes that long usage and wide marketing experience in addition to animal data are adequate evidence for classifying hexylresorcinol as a Category I ingredient for use on the mucous membranes.

(3) *Dosage:* Adults and children 3 years of age and older: Use a 0.05- to 0.1-percent concentration of hexylresorcinol in the form of a rinse, mouthwash, gargle, or spray no more than three to four times daily. Use a lozenge containing 2.0 to 4.0 mg of hexylresorcinol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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f. *Menthol.* The Panel concludes that menthol is safe and effective as an OTC anesthetic/analgesic active ingredient for use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Menthol is a secondary alcohol extracted from peppermint oil or made synthetically. Chemically, it is also known as hexahydrothymol and 3-paramenthanol. Menthol exists as colorless hexagonal crystals, as needlelike crystals in fused masses, or as a crystalline powder with a peppermint-like odor. Levo menthol melts between 41° and 44° C. Natural menthol is known as peppermint camphor. It may be levorotatory [1-menthol] or racemic (d,1-menthol). Menthol may be made synthetically by the hydrogenation (reduction) of thymol. Menthol is a secondary alcohol which can be considered to have been derived from the saturated hydrocarbon p-menthanol. Menthol is very slightly soluble in water, but soluble in alcohol, ether, chloroform, mineral oil, and in fixed and volatile oils (Refs. 1 and 2). Menthol may be fatal if ingested in large quantities. Doses of 1 to 2 g/kg may be fatal (Refs. 1 and 3).

(1) *Safety.* The Panel concludes that menthol is safe as an OTC active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Menthol causes sensitization in certain individuals. Symptoms include urticaria, erythema, and other cutaneous lesions. The sensitization index is low, however. Menthol has caused asphyxia in infants when applied locally for the treatment of coryza (runny nose).

Menthol was formerly used internally as a carminative. As the active ingredient of peppermint oil, it has found wide acceptance in candy, chewing gum, and cigarettes (Refs. 4 and 5). Menthol has had extensive use in inhalant preparations for the nose and throat. Inhalers containing menthol are commonly used for the relief of nasal congestion, headache, and neuralgia (Ref. 5).

Toxic effects from excessive ingestion of mentholated products can include nausea, abdominal pain, vomiting, and symptoms of central nervous system depression, such as dizziness, staggering gait, flushed face, sleepiness, slow respiration, and coma. The fatal dose of menthol in man is about 2 g (Refs. 6 and 7). Menthol is excreted in the bile and urine as a glucuronide (Ref. 8).

Rakieten, Rakieten, and Boyd (Ref. 9) studied the effects of menthol vapor on the upper respiratory tract of rats. The rats were exposed to different menthol vapor concentrations over a period of several months. Vapor in a range of less than 0.275 ppm showed no toxic effects, and there were no significant changes in skeletal muscle, skin, brain, or internal organs. Animals did show indications of lung irritation when exposed to the highest menthol concentrations.

In an unpublished study, Thomas (Ref. 10) used an ointment containing several volatile substances, including 2.5 percent menthol. It was applied to the abraded and intact skin of 223 subjects. After 48 hours, no instances of inflammation, wheal, hives, or primary irritation were seen.

Bliss and associates (Ref. 11) studied the effects of a 20-percent oil solution of menthol vigorously applied to the skin. They noted an intense and lasting cooling sensation followed by numbness, with a slight smarting sensation and hyperemia. Irritation beyond the rubefacient stage was not observed. Repeated topical application of mentholated products on the skin has been reported to give rise to hypersensitivity reactions (Refs. 8 and 12).

In young childrem nasal drops containing menthol may bring about spasm of the glottis. Cases of dangerous asphyxiation have been reported in infants following local application of menthol (Ref. 8). However, in a survey of approximately 124,000 infants receiving nasal drops containing essential oils, including menthol, no untoward effects were noted (Refs. 13 and 14).

It is the opinion of the Panel that although the actual number of adverse effects attributed to the internal anesthetic/analgesic use of menthol is relatively low, care should be taken to assure that safety is maintained through adequate packaging, labeling, and application.

(2) *Effectiveness.* The Panel concludes that menthol is effective as an OTC active ingredient for topical use on the mucous membranes when used within the dosage limit set forth below.

There are few well-controlled studies documenting the effectiveness of menthol as a topical anesthetic/analgesic for use on the mucous

membranes of the mouth and throat. However, due to its wide use and clinical acceptance, and on the basis of published reports in the literature (Refs. 12, 15, and 16), the Panel concludes that menthol is effective for such use.

Menthol belongs in the hydroxy-type group of local anesthetics It stimulates the nerves for the perception of cold and may depress the nerves for pain on the skin and mucous membranes (Ref. 1). In some cases, it merely substitutes one sensation for another.

Menthol is used as an antipruritic on the skin in a concentration range of 0.25 to 1.0 percent (Ref. 2). It also possesses counterirritant properties. When applied to the skin and mucous membranes of the mouth and throat, menthol stimulates the nerves for perception of cold while depressing those nerves which perceive pain.

Menthol is a feeble topical antimicrobial. Menthol is absorbed through the mucous membranes and penetrates the intact as well as the damaged skin. Menthol is indicated for the temporary relief of pain of the mucous membranes of the mouth and throat.

The duration of action of aqueous solutions of menthol used as rinses, mouthwashes, and gargles is usually short and seldom lasts more than 5 to 10 minutes. When incorporated in lozenges that slowly release the ingredient, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve pain of sore mouth or sore throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 0.04- to 2.0-percent concentration of menthol in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 2.0 to 20.0 mg of menthol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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g. *Phenol.* The Panel concludes that phenol is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Phenol is hydroxybenzene. Phenol was discovered in 1934 in coal tar by Ringe, who named it "carbolic acid." It was also once called phenic acid (Ref. 1). Phenol is a primary alcohol of the aromatic series and as such exerts a topical anesthetic action (Ref. 2). Although it may be obtained from coal tar, most of it is now prepared synthetically. The antimicrobial effectiveness of phenol was first demonstrated by Lister in 1857. Its clinical use at present is limited to use as a topical anesthetic and for cauterization (Ref. 3). Compounds less toxic than phenol are more effective antimicrobial agents (Ref. 1). Phenol exists as colorless to light-pink, needle-shaped crystals interlaced or separated, or as a white to light-pink crystalline mass (Ref. 4). It possesses an aromatic odor which is distinctive and differs from other aromatic alcohols. It gradually darkens on exposure to light and air. Phenol is liquified by warming or by the addition of 10 percent water. It is caustic if applied directly to tissues (Ref. 1). A concentrated solution of phenol and water has a strength of approximately 6 percent at room temperature. Phenol is very soluble in alcohol, glycerin, chloroform, ether, and fixed and volatile oils (Ref. 4). It is sparingly soluble in mineral oil. Solutions of phenol are oxidized and turn brown due to the formation of quinones (Ref. 1). Phenol forms a salt, phenolate sodium, with sodium hydroxide which is ionized and highly alkaline. One gram dissolves in about 5 mL of water. Phenol boils at about 182° C. It congeals at temperatures lower than 39° C. Phenol combines with camphor to form a substance known as camphor-phenol (Ref. 5). Whether or not this is a definite chemical complex or a solution of phenol in camphor has not been established with certainty, but the consensus seems to be that it is a complex. The substance releases free phenol slowly in small quantities. The presence of moisture hastens the process (Ref. 1).

(1) *Safety.* The Panel concludes that phenol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Concentrations greater than 1.5 percent in aqueous solutions are irritating and may cause sloughing and necrosis (Refs. 3 and 6). Phenol causes an area of blanching when applied in pure form to the skin or mucous membranes. A feeling of numbness develops. Later the area undergoes necrosis and sloughing (Ref. 1).

After oral ingestion or absorption from other sites from which it may pass into the systemic circulation, phenol is oxidized and conjugated with sulfuric, glucuronic, and other acids by the liver and excreted into the urine. Only small quantities of free phenol are excreted into the urine. Phenol is lipophilic and is readily absorbed through the intact and damaged skin and passes into the systemic circulation (Ref. 7). Absorption through the skin depends upon the area exposed rather than on the concentration (Refs. 3 and 8).

Phenol is readily absorbed after application to the mucous membranes. Concentrated solutions are toxic and cause death if ingested orally (Ref. 8). Phenol has been used for suicidal purposes. Cases of accidental poisoning have been common. The symptoms of toxicity usually develop rapidly and death has occurred within 2 or 4 hours after ingestion. Coma and collapse are the main manifestations of toxicity from large doses. After ingestion of small amounts, the most common symptoms are nausea, vomiting, collapse, pallor, cold sweats, and feeble pulse. Stupor ensues deepening into a comatose state with insensibility. Respirations are often rapid and shallow, irregular, and sometimes paroxysmal. Death results from respiratory arrest. Paralysis of both sensation and motion may occur. In some cases, violent clonic or epileptiform convulsions have occurred. The urine is generally scanty, albuminous, and greenish or black in color. The diagnosis is usually not difficult to make, since the odor of phenol can be detected on the breath and smelled in the smoky urine. White, corrugated spots are present on the mucous membranes of the mouth and throat due to the caustic action of the phenol.

The estimated fatal dose of phenol is approximately 15 g. However, death has been reported following the ingestion of as little as 1.5 g. Recovery has followed the ingestion of as much as 30 g. In the fatal cases, death usually occurs in less than 2 hours. Death usually occurs from respiratory failure, although in some instances cardiac failure has been the lethal terminal manifestation. The degree of toxicity depends upon the amount of phenol ingested. Its concentration is not an important consideration (Refs. 1 and 8). Chronic ingestion of phenol causes a dark brown discoloration of tissues most likely due to staining from quinones resulting from oxidation of phenol in the body. The cartilaginous tissues of the body appear to be affected more than other tissues (ochronosis).

(2) *Effectiveness.* The Panel concludes that phenol is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Phenol penetrates the sensory nerve endings and exerts its anesthetic effect in presumably the same manner as other local anesthetics/analgesics (Refs. 6 and 7). It is a lipophilic non-ionized polar substance and thought to act in the same manner as the "caine" type of topical anesthetics (Ref. 9). The hydrocarbon pole is lipophilic and orients into the lipid phase of the axon. The hydroxyl group is hydrophilic and orients into the water phase (Ref. 10). Phenol is acidic and forms salts with alkalis. It readily traverses epithelial barriers. Its absorption from the skin and mucous membranes does not depend upon the pH of the medium. A feeling of warmth and tingling ensues following the application of 5 percent phenol to the unabraded skin. Eventually, complete topical anesthesia/analgesia develops and the area becomes irritated. Phenol can, in concentrations exceeding 1.5 percent in water, be very irritating, and even caustic to the skin and mucous membranes and cause necrosis. Phenol possesses topical anesthetic/analgesic activity in concentrations of 0.5 to 1.5 percent. The blockade produced on the mucous membranes in concentrations of less than 1.5 percent is reversible. The latent period is short, being 1 to 2 minutes. Duration of anesthesia/analgesia on the mucous membranes of the mouth averages 5 to 10 minutes when used in the form of an aqueous solution as rinses, mouthwashes, and gargles. When incorporated in lozenges which slowly release the ingredient, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve pain of sore mouth or sore throat. As the drug is washed away by the saliva, the anesthetic/analgesia action recedes.

Duration of anesthesia/analgesia depends upon the site of application and concentration. Aqueous solutions stronger than 2 percent are too irritating for topical application. A 4-percent solution in glycerin is sometimes used and is said to be noncaustic. Because the glycerin helps retain the phenol when camphor is added to phenol, a liquid forms. Phenol forms a complex with camphor and holds it, releasing it slowly. Its rate of release depends upon the quantity of moisture present on the surface of application, temperature, and other factors. The quantity of phenol release from the mixture varies and depends upon the water content of the tissue. This apparently reduces the extent of the topical action and the absorption of phenol through its phenol-holding property (Ref. 5). The Panel questions the safety of such mixtures. Phenol is a keratolytic, neurolytic, and destructive agent in concentrations of 10 to 40 percent (Ref. 1).

Phenol is an anesthetic/analgesic to the mucous membranes. A 5-percent solution of phenol and water has definite topical anesthetic/analgesic action, but sloughing occurs in about 10 percent of the cases (Ref. 11).

A 5-percent solution of phenol in 95 percent alcohol is an efficient topical anesthetic/analgesic. Complete anesthesia results in 53 percent of the cases and partial anesthesia/analgesia in 47 percent of the cases.

However, sloughing or superficial necrosis occurred in 22 percent of cases studied. Phenol is soluble in oils and petrolatum which tend to hold it in solution and reduce its activity.

When phenol is combined with topical anesthetics/analgesics of the nitrogenous type which are active in the basic form, conversion of the nitrogenous base to the acid form occurs because phenol is an acid. This may nullify their action and not necessarily produce the anticipated effect or summation. The antimicrobial activity of phenol is due to its ability to coagulate proteins.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 0.5- to 1.5-percent concentration of phenol in aqueous solution in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 10 to 50 mg of phenol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. [See part III. paragraph B.1. below—Category I Labeling.]

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h. *Phenolate sodium (sodium phenolate).* The Panel concludes that phenolate sodium is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Phenolate sodium, also known as sodium phenolate, sodium phenate, sodium carbolate, sodium phenoxide, and phenol sodium, is the sodium salt of phenol (carbolic acid) (Ref. 1). Ordinarily, phenol exists in the enol form; that is, it is a benzene ring with a hydroxyl group. Phenol has high resonant energy and can revert to the keto form (Ref. 2). This keto-enol type of isomerization is encountered from time to time in various organic compounds. The keto form is less stable than the enol form. The sodium salt is formed with the keto form. One hydrogen atom on position 2 is replaced with the metalic ion. Phenols are consideed stronger acids than other alcohols or water, but are weaker acids than carboxylic acids. The dissociation constant of phenol is $1.3 \times 10^{10}$ as compared to $4.3 \times 10^{7}$ for carbonic acid. Phenol reacts with sodium hydroxide to form a water-soluble salt, but it will not interact with sodium carbonate to form a salt.

Phenolate sodium is a white to reddish deliquescent substance composed of rods or granules. It is readily decomposed by carbon dioxide to phenol and sodium carbonate if it stands in the air. It must be stored in tightly closed containers. Phenolate sodium is strongly alkaline and caustic. It is very soluble in water, and alcohol-aqueous solutions are strongly alkaline and caustic. Phenolate sodium releases 81 percent phenol on decomposition or acidification. Phenol is less acidic than carbonic acid. The therapeutic and toxic effects of phenolate sodium are due to the phenol released (Refs. 1, 2, and 3).

(1) *Safety.* The Panel concludes that phenolate sodium is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The safety considerations for phenolate sodium are the same as those for phenol, because it releases phenol, and its toxic effects are due to the phenol (Ref. 1). In addition, phenolate sodium may augment the caustic effects of phenol due to the presence of sodium hydroxide, from which it is formed, if concentrated solutions are ingested orally or applied topically. Phenolate sodium precipitates proteins and can, therefore, exert an antimicrobial effect, as does phenol. The Panel has considered the antimicrobial effects of phenol and phenolate sodium elsewhere in this document. (See part IV. paragraph B.3.s. below—Phenolate sodium.)

Phenolate sodium, in doses of 0.1 to 0.3 g, was formerly used to treat diarrhea.

(2) *Effectiveness.* The Panel concludes that phenolate sodium is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Aqueous solutions of phenolate sodium are alkaline and caustic, but dilute solutions can be used to obtain the same anesthetic/analgesic effect on the mucous membrane as phenol (Ref. 1). Since solutions containing phenolate sodium are alkaline, the effects of certain ingredients that are physiologically active in the form of a base are assured when they are used in combination with phenolate sodium. This is the case when phenolate sodium is combined with nitrogenous topical anesthetics/analgesics. The released phenol and alkali may enhance the effects of the latter compounds and maintain an alkaline medium. Phenolate sodium is not the sole ingredient in any of the products submitted to the Panel for consideration, but has been submitted in combination with other topical anesthetic/analgesic ingredients.

The duration of action of aqueous solutions of phenolate sodium used as rinses, mouthwashes, and gargles is usually short and seldom lasts more than 5 or 10 minutes. When incorporated in lozenges that slowly release the ingredient, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve pain of sore mouth or sore throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a concentration of sodium phenolate in aqueous solution, equivalent to a 0.5- to 1.5-percent concentration of phenol, in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge, containing a concentration of phenolate sodium which is equivalent to 10 to 50 mg of phenol, every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and suprvision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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i. *Salicyl alcohol.* The Panel concludes that salicyl alcohol is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The chemical structure of salicyl alcohol is ortho-hydroxy benzyl alcohol. Actually, it is benzyl alcohol with a hydroxyl group on the number 2 position of the benzene ring. Salicyl alcohol occurs in plates or crystalline powder which melts at 86 to 87° C. It sublimes at 100° C. It is soluble in water, 1 part in 15, and very soluble in alcohol, chloroform, ether, and benzene (Ref. 1).

Salicyl alcohol is the hydroxy type of topical anesthetic/analgesic. It is only suitable for surface anesthesia. As is the case with other alcohols, it is not suitable for injection because it is feeble and causes neurolysis and sloughing of parenteral tissues. It is a neutral substance and does not depend upon ionization or basicity for its pharmacologic effects.

(1) *Safety.* The Panel concludes that salicyl alcohol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

A study cited by Sollmann (Ref. 2) found that salicyl alcohol is the most effective, the least toxic, and least irritant of the phenyl carbanols. Its toxicity is much lower than that of the "caine" type drugs. Presumably, it is metabolized in the body. Toxicity data are not available. No fatalities in man have been recorded.

The Panel was unable to find any data on the acute animal toxicity and chronic human toxicity of salicyl alcohol except in certain formulations for OTC preparations because it has fallen into disuse. It appears to have no adverse effects on the mucous membranes in concentrations of 6 percent or less. It is not caustic as are the phenolic type of alcohols.

(2) *Effectiveness.* The Panel concludes that salicyl alcohol is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Salicyl alcohol is an effective topical anesthetic/analgesic on the mucous membranes in concentrations of 1 to 6 percent in aqueous solution. Its onset of action is rapid, requiring 2 to 3 minutes. The duration of action, like that of the other hydroxy-type local anesthetics/analgesics is brief. The duration of action of aqueous solutions of salicyl alcohol used as rinses, mouthwashes, and gargles is usually short and seldom last more than 5 to 10 minutes. When incorporated in lozenges that slowly release the ingredient, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve pain of sore mouth or sore throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 1.0- to 6.0-percent concentration of salicyl alcohol in aqueous solution in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 50 to 100 mg of salicyl alcohol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

**Reference**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1079, 1976.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, p. 278, 1948.

**Category I Labeling**

a. *Indication.* "For the temporary relief of occasional minor irritation, pain, sore, mouth, and sore throat."

b. *Warnings*—(1) *For all drug products containing oral health care anesthetic/analgesic active ingredients.* (i) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(ii) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(2) *For oral health care anesthetic/analgesic products used in the form of gargles, mouthwashes, and mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which anesthetic/analgesic active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are mesbranded.*

The Panel recommends that the Category II conditions be eliminated from OTC oral health care anesthetic drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredients**

Antipyrine.
Camphor.
Cresol.
Dibucaine.
Dibucaine hydrochloride.
Lidocaine.
Lidocaine hydrochloride.
Pyrilamine maleate.
Tetracaine.
Tetracaine hydrochloride.

a. *Antipyrine.* The Panel concludes that antipyrine is not safe and not effective for topical use as an anesthetic/analgesic on the mucous membranes of the mouth and throat.

Antipyrine is a pyrazolon derivative. Antipyrine is 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one. It exists as tubular crystals or as a white powder that is odorless and has a slightly bitter taste. It is also known as phenazone. It melts at 111° C (Ref. 1). One gram dissolves in less than 1 mL water, 1.3 mL alcohol, 1 mL chloroform, and 3.4 mL of ether. Aqueous solutions are neutral. Antipyrine was introducted as a medicine in 1887 (Ref. 2).

Antipyrine was synthesized by Knorr in 1883 in an attempt to prepare a substance that would be similar to quinine. It is administered orally as an anesthetic and antipyretic. It may be synthesized by several methods. One method involves the interaction of phenyl hydrizine and ethyl acetoacetate followed by methylation.

Antipyrine is incompatible with many substances, the most important of which are acetanilid, chloral, phenacetin, phenol, thymol, phenyl salicylate, sodium salicylate, various alkalis, alum, ammonia water, resorcinol, sodium bicarbonate, tannic acid, ferric chloride, and various other compounds (Ref. 3).

(1) *Safety.* The Panel concludes that antipyrine is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The oral $LD_{50}$ in rats is 1.8 g/kg. Large doses may cause nausea, vomiting, tremors, dizziness, weakness, diaphoresis, cyanosis, angioedema, and skin eruptions. It may produce methemoglobinemia in human beings, but this is rare. The skin eruptions may be macular, patchy, round or oval, varying in size, pink or dark purple, and persisting for a month or more after the drug has been withdrawn. Fixed pigmented areas occasionally result following its ingestion. Overdoses may produce stomatitis, drowsiness, convulsions, coma, and amaurosis (Ref. 3).

Antipyrine is absorbed from the mucous membranes of the mouth and throat. Some of its effects are systemic, although it allegedly has both local and systemic anesthetic effects. Swelling of the lips and the tongue and severe laryngeal edema interfering with respiration have occurred. A blue-grey coloration of the urine, which is green in reflected light, has been observed after large doses of antipyrine have been ingested (Refs. 2 and 3).

Antipyrine stimulates microsomal enzymes. It has been known to act additively with morphine. It combines with plasma proteins in a ratio of 1:8. Antipyrine is rapidly and completely absorbed from the gastrointestinal tract of man. Peak plasma levels are attained within 1 to 2 hours. It is slowly metabolized and disappears from the plasma at the rate of 6 percent per hour. The drug is rapidly metabolized in dogs and rabbits. The distribution depends on the water content of the tissue. It is metabolized by oxidation to form 4-hydroxy antipyrine (30 to 40 percent). This, in turn, is conjugated with glucuronic acid and excreted into the urine. Approximately 5 percent is excreted into the urine unchanged. Antipyrine does not produce euphoria, psychic or physical dependence, or withdrawal symptoms when administration is terminated. Cases of mild degrees of tolerance and habituation have been reported, but this has not been a problem. Antipyrine augments the doses of narcotics, analgesics, barbiturates, and hypnotics when ingested systemically.

Antipyrine is considered to be an unsafe drug because it produces severe cutaneous reactions. These are all believed to be due to sensitization. Of 394 cases of antipyrine poisoning reported prior to 1950, and reviewed by Greenberg (Ref. 4), 77 percent were of an allergic nature, 18 percent nonallergic, and in 5 percent the cause was undetermined. The most striking feature of the antipyrine hypersensitivity reaction is a fixed pigmented erythema. This was originally described by Brodie, et al. (Ref. 5). Ulceration of the buccal mucosa and erythematous pigmented lesions on the hands and the body have been noted. The Black race appears to be more susceptible to the stomatitis than other races. The majority of cases found in the literature concerning the toxicity of antipyrine indicate that the reported reactions are due to hypersensitivity.

The oral lethal dose of antipyrine in several species has been reported to be 1,000 mg/kg or more (Ref. 1). Thus, the main consideration of the Panel is the association between the use of antipyrine and the occurrence of fixed pigmented erythema of the skin and other types of skin reactions.

Antipyrine has fewer side effects than aspirin systemically. It does not interfere with the blood-clotting mechanisms as does aspirin. In addition, there is no evidence that antipyrine causes hepatotoxicity as does acetaminophen.

Antipyrine must not be confused with aminopyrine which, even though it is chemically allied, is known to cause irreversible agranulocytosis. Greenberg (Ref. 4) has indicated that only two cases of agranulocytosis due to antipyrine use were reported prior to 1950, and even in these it was not conclusive that antipyrine was the causative factor. No other cases have been reported since that time. Antipyrine, though closely related chemically to aminopyrine, is metabolized in a different manner, which is a possible explanation for differences in the propensity of aminopyrine to produce agranulocytosis.

The Panel has read with interest the comments of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products in which disagreement on antipyrine safety resulted in submission of both a majority and a minority report (42 FR 35436–35439). That Panel agreed that antipyrine may have merit and that, in spite of its long-term use in medicine, it has not been adequately evaluated for safety and effectiveness based on data from controlled studies. The minority felt that testing would be hazardous because of the known side effects due to sensitivity. The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products referred to the position of FDA concerning the use of antipyrine as an analgesic in earwax softening preparations. That Panel, in its review of OTC topical otic drug products, published in the **Federal Register** of December 16, 1977 (42 FR 63564), recommended that such preparations be available by prescription only and not be available OTC.

(2) *Effectiveness.* The Panel concludes that antipyrine is not effective as an OTC anesthetics/analgesics active ingredient for topical use on the mucous membranes of the mouth and throat.

There are no data substantiating the fact that antipyrine acts as a stabilizer of the axonal membrane as do the topical local anesthetics. There are data indicating that antipyrine enhances the blockade caused by cocaine on isolated nerves in frogs, but in does not by itself produce a neuronal blockade.

Antipyrine is a anesthetic and a mild antipyretic systemically. Topically, antipyrine has been reported to be a feeble anesthetic and antiseptic (Ref. 3) and also to have some anesthetic effect on nerve endings (Refs. 2 and 6). It may cause constriction of the superficial blood vessels. Antipyrine has been used for the treatment of inflammatory conditions of the mucous membranes of the mouth and throat and for laryngitis in concentrations ranging from 5 to 15 percent. A solution of antipyrine composed of 5.4 percent antipyrine and 1.4 percent benzocaine in glycerin was formerly used for the treatment of acute otitis media (inflammation of the middle ear). Antipyrine has been used as a styptic for nasal hemorrhage. Antipyrine has a feeble antimicrobial effect, but this is of no consequence in considering such effects on the mucous membranes of the mouth and throat.

(3) *Evaluation.* The Panel concludes that antipyrine is not safe because it causes sensitization and adverse systemic reactions. In addition, antipyrine apparently manifests no significant topical anesthetic effects.

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b. *Camphor.* The Panel concludes that camphor is not safe and not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Camphor is a member of a cyclic group of hydroaromatic substances known as terpenes (Refs. 1 and 2). Camphor is 2-bornanone, a 2-ketone of heptane, which is naturally occurring in the camphor tree (*Cinnamum camphora*), an evergreen native to Eastern Asia. Natural camphor is obtained from all parts of the camphor tree. Camphor is also made synthetically from alpha pinene, a constitutent of turpentine. Approximately three-fourths of the camphor used is prepared synthetically. Natural camphor is optically active. Natural camphor is dextrorotatory, while the synthetic preparation is racemic and optically inactive. Both forms are pharmacologically active. Camphor melts at 174° to 177° C at atmospheric pressure. It sublimes readily. At 25° C, 1 g dissolves in 800 mL water, 1 mL ether, 1 mL alcohol, 0.5 mL chloroform, 0.4 mL acetone, and 1.5 mL turnpentine. Camphor, since it is a ketone, is converted by reduction to borneol, a secondary alcohol. Camphor has a peculiar tenacity and cannot be powdered in a mortar until it is moistened with an organic solvent. It liquifies when tribturated with menthol, thymol, phenol, and resorcinol. It is not compatible with oxidants such as potassium permanganate. Camphor forms complexes with cresol (camphor metacresol) from which both ingredients and other phenols can be released. Camphor is freely miscible with volatile and fixed oils. When applied to the skin and mucous membranes, camphor produces a feeling of warmth and provides a mild local anesthetic action that may be followed by numbness (Refs. 1 and 3).

Several camphor products are described in the official compendia. Camphor liniment, as listed in "National Formulary X", contains 20 percent camphor in cottonseed oil. This preparation is commonly called "camphorated oil." Other topical products containing camphor are camphor and soap liniment (4.5 percent

camphor) in "United States Pharmacopeia XIII", camphor spirit (10 percent camphor) in "National Formulary X", and camphor ointment (20 percent camphor) in "National Formulary IX" (Ref. N–6).

(1) *Safety.* The Panel concludes that camphor is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Camphor is absorbed from the mucous membranes and at the mucocutaneous junctions. Camphor is absorbed if injected subcutaneously. It is also absorbed from intact and damaged skin since it is nonionized and lipophilic. Excessive oral doses may be fatal (Ref. 3). Camphor is metabolized when ingested orally or assimilated by other routes. The camphor is first oxidized by the liver to campherol, and the campherol is then conjugated with glucuronic acid by the liver. The conjugate is excreted in the urine.

Camphor's minimal lethal/dose for rabbits is 2 g/kg orally. The median lethal dose ($LD_{50}$) subcutaneously for rats is 2.2 g/kg. The oral median lethal dose for guinea pigs is 180 mg/kg. In mice, the $LD_{50}$ is 30 mg/100 g when administered intraperitoneally. The estimated minimal lethal dose for humans when ingested orally is 2 g. One adult survived ingestion of 1.5 g of camphor. Ingesting 0.7 to 1.0 g of camphorated oil proved fatal to a child (Ref. 5). Accidental poisoning has occured from ingesting the oil when it has erroneously been administered for castor oil. Cases of poisoning continue to be reported. The Panel considered various reports and editorials submitted to it concerning the toxicity and frequency of poisonings from camphor-containing preparations, particularly in children. The Panel has taken cognizance of these cases and those that continue to occur. However, the Panel is unaware of any case of poisoning that has occurred from topical administration on the skin in spite of the fact that camphor is known to penetrate the skin due to its lipophilic nature. The Panel is also aware of the fact that camphor is readily absorbed from the mucous membranes of the mouth, throat, and gastrointestinal tract.

Camphor is used as a component of paregoric (camphorated tincture of opium), which is widely used as an antidiarrheal in adults and children, and as a sedative and anesthetic in infants and children. However, no documented justification for its use systemically or topically on the mucous membranes has been found. The Panel, therefore, considers camphor not safe as a topical anesthetic/analgesic on the mucous membranes. Camphor in oil was once used parenterally as an analeptic, but it has long since been abandoned for this purpose. Systemically, camphor stimulates the central nervous system. Toxic doses produce convulsions which may be fatal. Camphor is not a common skin sensitizer but can, in concentrations above 3 percent, be an irritant. It is used as a counterirritant on the skin in topical antirheumatic preparations (Ref. 3). Its sensitizing potential on the mucous membranes is not known.

(2) *Effectiveness.* The Panel concludes that camphor is not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The Advisory Review Panel on OTC External Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products has evaluated the topical use of camphor as an analgesic, an anesthetic, and as a counterirritant (44 FR 69802). That Panel's recommendations and conclusions were published in the **Federal Register** of December 4, 1979 (44 FR 69768). In concentrations of 3 percent or less by weight, camphor is an effective antipruritic and relieves the discomfort due to skin lesions characterized by itching and burning on the skin at the site of application. It is believed to act upon sensory receptors in the skin and mucous membranes in the same manner as the hydroxy or alcohol types of topical anesthetics even though it is a ketone. In concentrations exceeding 3 percent, particularly if combined with other ingredients that produce counterirritation, camphor stimulates the nerve endings in the skin and induces relief of pain and discomfort in muscles, joints, and other subcutaneous structures at a site distant to its application on the skin. The Panel does not find any data establishing camphor as an effective topical anesthetic/analgesic ingredient for topical use on the mucous membranes of the mouth and throat. When camphor is injected internally it produces a sensation of warmth. Numerous clinical reports regarding the ability of camphor to relieve cutaneous itch are available (Refs. 1, 3, and 6).

Camphor most likely exerts its anesthetic effects in a manner similar to that manifested by the hydroxy or alcohol type of compounds. When applied to the skin or mucous membranes, it produces a sense of warmth followed by a sensation of numbness. Topically, camphor is weakly antiseptic, but this attribute is of no practical significance as far as effective antimicrobial activity in the oral cavity is concerned. The odor of camphor may play a role in the relief of pain (Refs. 1, 3, and 6). The psychological component of the effect of drugs in causing pain relief by their placebo effect cannot be ignored when used topically on the skin, but it is doubtful that this mechanism operates when the drug is used on the mucous membranes.

(3) *Evaluation.* There are no well-documented studies that show that camphor is an effective active ingredient for topical use on the muscous membranes of the mouth and throat in a dosage range that does not irritate tissues. The fact that camphor is effective when used topically on the skin does not support the contention that it is equally as useful on the mucous membranes. Camphor is readily absorbed and has resulted in fatalities when taken internally and is therefore not a safe ingredient for use on the mucous membranes.

**References**

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c. *Cresol.* The Panel concludes that cresol is not safe and not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The description of cresol and its safety appears in detail in the section on antimicrobial agents described below. (See part IV. paragraph B.2.d. below—Cresol).

(1) *Safety.* The Panel concludes that cresol is not safe as an OTC anesthetic/

analgesic active ingredient for topical use on the mouth and throat.

(2) *Effectiveness.* The Panel concludes that cresol is not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mouth and throat.

Since cresol is an aromatic alcohol and structurally and chemically similar to phenol, it behaves like phenol pharmacologically (Refs. 1, 2, and 3). Cresol is rapidly absorbed from the skin and mucous membranes and is somewhat less toxic than phenol, but exerts similar caustic and protein-denaturing qualities. When applied locally to the skin, cresol causes an erythema and burning sensation followed by numbness (Ref. 4). It acts in the same manner as phenol and destroys tissue, cauterizing the area of application.

Dilute solutions of cresol possess a topical anesthetic activity similar to that of the hydroxy type of local anesthetics. It is, however, not recommended or used for this purpose.

(3) *Evaluation.* Cresol is a phenolic derivative with antimicrobial and topical anesthetic activity. The Panel concludes that cresol is not safe for use as an anesthetic/analgesic on the mucous membranes of the mouth or throat.

**References**

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d. *Dibucaine.* The Panel concludes that dibucaine is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Dibucaine is a synthetic topical anesthetic of the "caine" type, derived from quinoline (Ref. 1). It was introduced in 1929 by McElwain (Refs. 2 and 3). Its chemical name is butly oxychinchoninic acid diethly ethylenediamide. It is in no way related to quinine as its name may suggest. It is not an ester, as are benzocaine and tetracaine, but is an amide. It was one of the first of the amides to be adopted for clinical use. Its chemical configuration follows closely the general characteristics of the "caine" type of drugs (Refs. 2 and 4).

Dibucaine is a tertiary amine and, therfore, a base that reacts with acids to form salts, the most common of which is the hydrochloride salt. The free base is a colorless, almost odorless powder that melts at 63° to 64° C. The powder darkens on exposure to air. As is the case with other bases of the topical anesthetics of the "caine" type, it is poorly soluble in water. It is readily soluble in ether, various other organic solvents, in fatty oils and loeaginous bases.

The hydrochloride salt is a white, tasteless powder which melts at 90° to 98° C. The melting point is not sharp. It is very soluble in water (one part dissolves in 0.5 part water) and in organic solvents, such as benzene, acetone, and chloroform. It is insoluble in ethers and oils. Aqueous solutions have a pH range of 6.2 to 6.5. Alkaline substances, such as the hydroxides, carbonates, and bicarbonates, readily precipitate the base from aqueous solutions. Solutions must be prepared in distilled water and stored in alkaline-free glass; otherwise, the drug precipitates out due to the reaction with the alkali in the glass. Solutions of salts of dibucaine are stable when boiled. Dibucaine is compatible with epinephrine. The general "United States Pharmacopeia" name and the one that is accepted is dibucaine. The hydrochloride salt is more stable thant the base (Refs. 1, 2, 4, and 5). Solubility of the salt in oils or nonwater-soluble bases is poor. It is soluble in glycols.

(1) *Safety.* The Panel concludes that dibucaine is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Dibucaine is a synthetic topical anesthetic of the amide type derived from quinoline (Refs. 2 and 6). It is a base that forms salts with various acids. The most frequently used salt is the hydrochloride. Dibucaine is a "caine" type drug and closely follows the characteristic chemical configuration of this type drug in having an amino group, dimethylene chain, and aromatic nucleus. Dibucaine is approximately 15 times more potent and toxic than procaine, which has been used as the reference standard in clinical studies. Since it is more potent and more toxic on a parallel basis, only one-fifteenth would be required to achieve the same effect as procaine. The absolute toxicity is 15, but the relative toxicity compared to procaine is 1. Toxicity, of course, depends upon the site and mode of application, and the vascularity of the tissues as well as the mode and rate of biotransformation. The lethal dose in human beings, therefore, is unknown. It is one of the most potent and longest lasting of the topical anesthetics. In mice, the acute intravenous $LD_{50}$ is 2.8 mg/kg compared to 21 mg/kg for procaine and 11 mg/kg for cocaine. In rabbits, dibucaine is six times as toxic as cocaine given intravenously (Ref. 7). Dibucaine produces central nervous system stimulation and myocardial depression characteristic of the "caine" type of drugs when recommended doses are exceeded and high plasma levels result. Fatalities have been reported from the use of the maximal tolerable dose following infiltration, perineural injection, or topical application to the mucous membranes. Fatalities have not been reported following the use of dibucaine-containing products after application to the mucous membranes as a prescription item. Ten cases of acute intoxication, five of which were fatal, have been reported after the oral ingestion of dibucaine. In nine of those cases, the drug was prescribed for rectal use; in one case intoxication followed the use of ointments and creams marketed OTC for topical use. Five fatalities due to accidental ingestion of OTC ointments by children have been reported. These cases were documented in an adverse reaction reporting system extending from 1951 to 1972 (Ref. 8).

During the long period of marketing experience, reactions on the skin and mucous membranes due to irritancy and allergy have been low. Patch testing in controlled studies in humans, and a review of the literature by Lane and Luikart (Ref. 9) reveal that the incidence of sensitization reactions is low and no greater than that observed with procaine, tetracaine, benzocaine, and cyclomethycaine. Dibucaine can act as a hapten and be antigenic. Anaphylactic and other allergic types of reactions are possible, but have not been reported after topical use on the skin or mucous membranes after rectal and oral use.

Dibucaine has been alluded to as a "highly toxic" anesthetic by physicians. Relatively speaking, however, it is no more toxic than procaine, tetracaine, lidocaine, and similarly acting drugs if used in proper dosage and with the same precautions. Its chief danger lies in its potency, since one-tenth to one-fifteenth as much would be required to produce a toxic reaction compared to lidocaine or procaine. Too liberal use of a preparation from topical application to mucous membranes or over wide areas of damaged or abraded skin from which the drug is readily absorbed could result in severe and often fatal systemic reactions. Absorption from the oral cavity can be rapid and result in high plasma levels. Systemic absorption may

result in convulsions, myocardial depression, and death (Ref. 5). Dibucaine must not be ingested orally because it is absorbed from the intestines. Sensitization can occur but is uncommon.

(2) *Effectiveness.* The Panel concludes that dibucaine is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Dibucaine is one of the most potent and longest lasting topical anesthetics. It is approximately 15 times more potent than procaine and 3 to 6 times more potent than cocaine. As is the case with other topical anesthetics, it acts by stabilizing the neuronal membrane of the pain receptors in the mucous membranes. It has been used extensively for spinal anesthesia, topical anesthesia on the mucous membranes and skin, and to a lesser extent for infiltration and nerve blocking. Its period of latency when used intrathecally may be as long as 10 minutes. Its duration of action introthecally is approximately 3 hours. This latency and long duration of action are also reflected when used by other routes (Ref. 2). The base readily penetrates the intact skin and mucous membranes. It acts superficially on the mucous membranes and not on the deeper structures below. The concentrations absorbed systemically from the mucous membranes are significant and may result in high plasma levels, which may cause fatal systemic reactions. In view of this, the Panel regards the drug as too hazardous for OTC use in the oral cavity and emphasizes that it should be administered by a physician familiar with its hazards and use.

(3) *Evaluation.* The Panel concludes that dibucaine in not a suitable OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat because of its rapid absorption which may result in fatal systemic toxicity.

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e. *Dibucaine hydrochloride.* The Panel concludes that dibucaine hydrochloride is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The general characteristics of dibucaine hydrochloride have been discussed elsewhere in this document. (See part III. paragraph B.2.d. above—Dibucaine.)

(1) *Safety.* The Panel concludes that dibucaine hydrochloride is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The remarks above concerning the safety of dibucaine base are also applicable to the hydrochloride. (See part III. paragraph B.2.d. (1) above—Safety.) As is the case with salts of other topical anesthetics, dibucaine hydrochloride penetrates epithelial barriers and exerts an anesthetic effect on pain receptors and other receptors with which it comes into contact and on receptors in structures immediately beneath the epithelial layers. It passes into the tissue fluids and gains access to the systemic circulation. Since dibucaine is approximately 15 times more potent and toxic than procaine, the quantity used in an OTC preparation could result in high plasma levels and serious systemic responses. Reactions from the use of therapeutic doses on the mucous membranes are uncommon but do occur (Ref. 1).

Systemic absorption can result in convulsions, myocardial depression, or death (Ref. 1). Dibucaine hydrochloride is readily absorbed from the mucous membranes. It is also absorbed from open lesions or broken or abraded skin, but not from the intact epithelial barriers (Refs. 2 and 3). The possibility that sufficient quantities may be absorbed from mucous membranes and cause fatal reactions is great. The Panel also calls attention to the greater solubility of the hydrochloride in the water of tissue fluids than the solubility of the base. However, the hazard from rapid aborption from either the salt or the base is almost equally as great.

Sensitization can occur and has been reported but is uncommon.

(2) *Effectiveness.* The Panel concludes that dibucaine hydrochloride is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Dibucaine hydrochloride is converted to the base when absorbed by mucous membranes from the buffering mechanisms in the tissues. Its mechanism of action is similar to dibucaine base.

There are well-controlled studies documenting the effectiveness of dibucaine hydrochloride as an anesthetic/analgesic for topical use of the mucous membranes of the mouth and throat. Dibucaine hydrochloride enjoys wide use and clinical acceptance. However, based upon published reports in the literature and due to the danger of fatal reactions, the Panel concludes that dibucaine hydrochloride should be used topically as an anesthetic/analgesic active ingredient on the mucous membranes as a prescription drug only and not for OTC use.

(3) *Evaluation.* The Panel concludes that dibucaine hydrochloride is not a suitable OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat because of its rapid absorption which can result in fatal systemic toxicity.

**References**

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f. *Lidocaine.* The Panel concludes that lidocaine is effective but not safe as an OTC anesthetic/analgesic for topical use on the mucous membranes of the mouth and throat.

Lidocaine is an amide type of topical anesthetic and thus differs from tetracaine, benzocaine, and procaine which are esters of paraminobenzoic acid. Lidocaine is 2-(diethylamino)-2', 6'-acetoxylidide (Ref. 1). It can also be considered an acetamide with one of the hydrogen atoms on the amino group of the amide portion of the compound replaced by a dimethyl aniline group

and one of the hydrogen atoms on the terminal carbon atom replaced by a nitrogen atom with two ethyl groups. It is a tertiary amine and is, therefore, a base that forms salts with acids (Ref. 2). The salt used clinically is the hydrochloride.

Lidocaine was synthesized by Lofgren in 1946 in Sweden (Ref. 3). Lidocaine base is a white to slightly yellow crystalline powder having a characteristic aromatic odor. It is practically insoluble in water, very soluble in alcohol and chloroform, freely soluble in ether, and dissolves in oils. Lidocaine is more lipophilic than procaine. Lidocaine base melts between 66° and 69° C (Ref. 4). Lidocaine base for use as a topical anesthetic/analgesic on the mucous membranes is incorporated in water-miscible solvents such as polyethylene glycol, propylene glycol, and methyl cellulose (Ref. 5). It may also be used in aqueous solutions.

Lidocaine salts are highly stable in vitro. The hydrochloride endures 8 hours when boiled with 30-percent hydrochloric acid, or after lengthy heating with alcohol and potassium hydroxide (Ref. 2). However, it is readily metabolized in the body. Up to 11 percent of the usual doses used for regional block in humans are recoverable in the urine within 4 hours (Ref. 6). The hydrochloride salt is not easily isolated from the solution.

(1) *Safety.* The Panel concludes that lidocaine is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Although lidocaine base is poorly soluble in water, it is readily absorbed when applied over mucous membranes. If sufficient quantities are absorbed, plasma levels may be attained that result in systemic pharmacological reactions characteristic of the "caine" type drugs which may be fatal (Ref. 7). Reactions due to systemic absorption are of the central nervous system type and the cardiovascular type. Stimulation of the cortex occurs first, followed by depression of not only the cerebral cortex, but lower centers as well (Ref. 8). Slow onset of a reaction causes stimulation followed by depression leading to drowsiness, nervousness, dizziness, blurred vision, nausea, tremors, convulsions, and respiratory arrest. When the onset is rapid, central nervous system depression occurs, leading primarily to unconsciousness which may be followed by respiratory arrest (Ref. 7). Myocardial depression and cardiac arrest may occur simultaneously. In addition, a fall in blood pressure and intercostal paralysis is regarded as a potential hazard resulting from high plasma levels (Ref. 9).

Lidocaine is used intravenously in small quantities by internists. Lidocaine has useful antiarrhythmic activity attributed to an increase of the electrical stimulation threshold of the ventricle during diastole. The antiarrhythmic action is similar to that of procainamide and quinidine but, because of its short duration of action, lidocaine hydrochloride must be given by continuous intravenous infusion if the action is to be sustained. The antiarrhythmic action usually develops within a few minutes and has a duration of 10 to 20 minutes, following a single intravenous injection of 50 to 100 mg. When it is used intravenously at the rate of 10 to 45 microgram/kilogram (μg/kg) of body weight per minute, the antiarrhythmic action begins to develop in 10 to 20 minutes. Blood levels of 1.0 to 2.5 μg/ml appear to be required for suppression of ventricular arrhythmias. These blood levels may be attained with an intravenous priming dose or by continuous infusion of the drug. Blood levels exceeding 5 μg/ml may, however, prove toxic and cause convulsions and cardiac depression. Constant electrocardiograph monitoring is used to avoid overdosage and toxicity.

Manufacturers of lidocaine indicate that its specific indication is for the drug management of ventricular arrhythmias occurring during cardiac manipulation, such as cardiac surgery. It is used for life-threatening arrhythmias, particularly those which are ventricular in origin, such as occur during acute myocardial infarction (Refs. 10 and 11).

Approximately 90 percent of a dose of lidocaine is metabolized by the enzmes in the microsomes of the liver within 4 to 5 hours, and the metabolites are excreted along with 10 percent of the unchanged drug in the urine. Lidocaine is metabolized by several metabolic pathways in the liver. The enzymes involved are oxidases and amidases. Several metabolites have recently been found which produce convulsant activity. These may account for delayed reactions due to cumulative effects. Lidocaine is not hydrolyzed by the plasma cholinesterases as are tetracaine, procaine, and other esters of aminobenzoic acid (Refs. 6 and 8).

Lidocaine base or its salts are not irritating to intact or abraded skin (Ref. 12). Lidocaine can produce sensitization after repeated contact, as do the "caine" type drugs, despite statements made to the contrary. However, the incidence of sensitization is low (Ref. 7). The statement has appeared in the medical literature that the amide type of the "caine" topical anesthetics is devoid of sensitizing potential (Ref. 8). Such a statement cannot be supported either on a theoretical or factual basis. Most soluble drugs are capable of acting as haptens and forming antigens. They can produce antigens that stimulate production of immune bodies of the IgE type which cause allergic reactions in susceptible individuals. Anaphylaxis has been reported after application of lidocaine to the mucous membranes and infiltration. One case has come to the Panel's attention in which an anaphylactic reaction occurred following application to the skin (Ref. 13). The report, however, does not state whether the quantity, which was said to be minute, was injected to raise a skin wheal or applied by a patch or scratch test. In another case (Ref. 13), a female patient who alleged that she was allergic to lidocaine was tested for this allergy by instilling one drop into the conjunctival sac. The patient developed immediate syncope, circulatory collapse occurred, and then severe shock. After 2 hours of treatment with vasopressors, antihistamines, and steroids, she recovered.

(2) *Effectiveness.* The Panel concludes that lidocaine is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

There are well-controlled studies documenting the effectiveness of lidocaine as an anesthetic/analgesic for topical use on the mucous membranes of the mouth and throat. Lidocaine enjoys wide use and clinical acceptance, and its effectiveness has been documented in published reports in the literature, the Panel concludes that lidocaine should be available by prescription, and not be used as an OTC anesthetic/analgesic.

Lidocaine is approximately twice as potent and toxic as procaine on a weight bases (Ref. 7). The onset of anesthesia is rapid, after injection, requiring less than 1 minute. The onset of action when used on mucous membranes is 1 to 2 minutes. The base is poorly soluble in water but soluble in lipid substances such as glycols and similar types of solvents. The base penetrates the intact skin and exerts an anesthetic and antipruritic action in the skin (Ref. 12). The salts do not.

Lidocaine base is an effective topical anesthetic/analgesic on the mucous membranes. When properly formulated, with ingredients that insure its stability and continuous contact with an epithelial surface, it provides prolonged anesthesia. The pain-relieving action of lidocaine, as is the case with other topical anesthetics of the "caine" type, is entirely within the mucous

membranes. The quantity circulating in the blood is insufficient to provide anesthesia to parts of the body distal to the site of application in structures beneath the mucous membranes. Lidocaine blocks transmission at nerve endings by stabilizing the neuronal membrane in the same manner as do other topical anesthetics of the "caine" type (Ref. 2). Anesthesia of the mucous membranes persists for 20 to 30 minutes after application to a mucous surface.

(3) *Evaluation.* Lidocaine is an effective anesthetic/analgesic for topical use on the mucous membranes, but is rapidly absorbed and capable of producing toxic systemic reactions that can be fatal. The Panel concludes that it should remain a prescription item and concludes it is not safe as an OTC product for self-medication by a consumer.

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g. *Lidocaine hydrochloride.* The Panel concludes that lidocaine hydrochloride is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Lidocaine hydrochloride is the salt of lidocaine base, a tertiary amine. The chemistry of lidocaine base has been described elsewhere in this document. (See part III. paragraph B.2.f. above—Lidocaine.) Lidocaine hydrochloride is a white crystalline powder with a slightly bitter taste. It melts between 74° and 79° C. It is very soluble in water, alcohol, and chloroform, but is insoluble in ether (Refs. 1 and 2). Lidocaine hydrochloride is very stable in vitro and withstands boiling in 30 percent hydrochloric acid for 8 hours or more. Aqueous solutions are acidic in reaction, the pH ranging from 5 to 6.4 (Ref. 3). The salt is highly ionized and not lipophilic. When injected into the tissues or applied on mucous membranes it is converted to the free base due to the buffering mechanisms present in the tissues. The free base is the physiologically active form of the drug. The nitrogen atom on the cation of lidocaine hydrochloride is converted from a tertiary atom to a quaternary atom (Ref. 4).

(1) *Safety.* The Panel concludes that lidocaine hydrochloride is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Lidocaine hydrochloride is very soluble in water. It is twice as potent and twice as toxic as procaine. It is readily absorbed from the mucous membranes of the mouth, pharynx, trachea, and bronchi. Absorption is followed by significantly perceptible blood levels that result in systemic toxicity if lidocaine hydrochloride is applied liberally.

Human toxicity varies with individual tolerance, age, sex, health status, and vascularity of the tissues. Convulsions and cardiac depression may occur if applied in excessive quantities (Refs. 5 and 6). The potential for sensitization exists, as with any other drugs, but it is not greater than with other topical anesthetics (Refs. 2 and 6). Topical irritancy is low, and rashes and other cutaneous lesions have not been reported. As is the case with other nitrogenous local anesthetics, lidocaine is dispensed as the hydrochloride salt because of its greater stability and ease of handling.

(2) *Effectiveness.* The Panel concludes that lidocaine hydrochloride is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The hydrochloride salt is acidic, is highly ionized, and is not strongly lipophilic; therefore, it does not readily penetrate epithelial barriers. It is active when it is converted to the base by the buffering mechanisms of the tissues. This occurs when it is injected perineurally or when it is applied to the mucous membranes.

Lidocaine acts by stabilizing the axonal membrane and preventing conduction in the nerve fibers connecting with receptors for pain and other stimuli in the skin. Adriani and Zepernick (Ref. 7) found that it rated fifth among 40 topical anesthetics tested on the tip of the tongue in deadening pain due to electrical stimulation. The free base is the physiologically active form. Additional data on effectiveness of lidocaine is described elsewhere in this document. (See part III. paragraph B.2.f. (2) above—Effectiveness.)

(3) *Evaluation.* Although lidocaine hydrochloride is an effective anesthetic, it is not safe for oral health care preparations intended for pain relief because it may be absorbed rapidly and cause tremors and often fatal toxic reactions, unless used with extreme caution.

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h. *Pyrilamine maleate.* The Panel concludes that pyrilamine maleate is safe but not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Pyrilamine maleate is 20(2-dimethyl-aminoethyl) (para-methoxybenzyl)amino pyridine bimaleate. It is an antihistaminic drug that is a derivative of ethylene diamine. Pyrilamine maleate was first synthesized in France in 1946 and introduced as an antihistamine drug. It

was one of the first antihistaminic drugs to be introduced and has actions and uses of the class of therapeutic agents known as the antihistamines.

Pyrilamine maleate is a white crystalline powder with a faint odor. One gram dissolves in 0.5 mL water, 3 mL alcohol, and 2 mL chloroform. It is only slightly soluble in ether. It melts between 99° and 103° C. Pyrilamine maleate in a 10-percent solution has a pH of approximately 5.1 (Refs. 1 and 2).

(1) *Safety.* The Panel concludes that pyrilamine maleate is safe as an anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Pyrilamine maleate is readily absorbed from the gastrointestinal tract. It is also absorbed to a variable extent, depending upon concentration and area exposed, from the mucous membranes of the mouth and throat. The absorbed drug in this manner produces systemic effects. In recommended doses, there is a remarkable lack of systemic toxicity (Refs. 3 and 4). Animal data on toxicity were not available to the Panel. The toxicity, according to Gosselin et al. (Ref. 5), is between 4 and 5. The most common side effect of pyrilamine maleate is sedation manifested by drowsiness. The sedative effect of the antihistamines is not unpleasant. In certain patients, particularly those of the ethylene-diamine type, antihistamines may have a stimulating effect. Other side effects of overdosage of pyrilamine maleate include euphoria, nervousness, insomnia, tremors, blurring of vision, diplopia, fatigue, loss of appetite, nausea, vomiting, epigastric distress, etc. If doses are increased, sedation may be replaced by irritability leading to convulsions, hyperpyrexia, and even death resulting from respiratory arrest (Ref. 6). Children are more likely to develop excitation, erythema, and marked hyperthermia with toxic doses. Milder forms of toxic reactions consist of visual disturbances, dizziness, confusion, irritability, and difficulty in coordination. Pyrilamine maleate may produce skin rashes and urticaria (hives) after oral administration or topical application (Refs. 7 and 8). Since pyrilamine maleate can act as a hapten, it can produce allergic reactions even though it is used for the treatment of patients with allergic conditions (Refs. 9 and 10). The simultaneous use of pyrilamine and alcohol or other central nervous system depressants has an additive effect which causes an enhancement of the depression (Refs. 3, 4, and 11).

(2) *Effectiveness.* The Panel concludes that pyrilamine maleate is not an effective anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Antihistamines have structures that are closely allied to structures of local anesthetics and may have anesthetic properties. This action has not been ascribed to pyrilamine (Ref. 10). The antihistamines, besides being competitive antagonists of histamine, also have, in addition to the central nervous system effect, anticholinergic and antiserotonin action (Ref. 12). Pyrilamine maleate may have a cocaine-like effect on catecholamine uptake. Pyrilamine maleate is readily absorbed from the gastrointestinal tract after oral administration. Its action is manifest within 15 to 20 minutes. The peak effect is attained in 1 hour, and it has a duration of 3 to 6 hours. Practically all the drug is metabolized and excreted in the urine unchanged (Ref. 13). It is the consensus of the Panel that any beneficial effects drived from pyrilamine maleate applied topically on the mucous membranes of the mouth and throat are due to its systemic effect after absorption, if sufficient quantities are applied, and not to any local effect on pain receptors (Refs. 3 and 13).

(3) *Evaluation.* The Panel concludes that pyrilamine maleate has no significant anesthetic/analgesic effect on the mucous membranes of the mouth and throat.

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i. *Tetracaine.* The Panel concludes that tetracaine is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Tetracaine is one of the numerous soluble aminobenozic acid esters possessing topical anesthetic activity. Tetracaine is closely allied to procaine in chemical structure (Ref. 1). It has been available since 1932 for spinal, epidural nerve blocks, and topical anesthesia. In the structure of tetracaine, a butyl group is substituted for one of the hydrogen atoms of the amino group on the benzene ring of procaine. The two ethyl groups on the nitrogen atom of the amino ethanol portion of the procaine molecule are replaced by methyl groups. The molecule of tetracaine conforms to the general configuration characteristic of the "caine" type drugs that have an aromatic nucleus, an ester linkage, an intervening dimethylene chain, and a tertiary nitrogen atom. Shortening the ethyl groups to methyl groups and replacing the hydrogen atom on the amino group with a butyl radical increases the potency and toxicity of tetracaine approximately 10 times compared to that of procaine (Refs. 1 and 3). Tetracaine manifests topical anesthetic activity both internally on the mucous membranes and externally on the skin. The duration of action is approximately two to two-and-one-half times that of procaine. This is due to the fact that the protein-binding activity and the lipid solubility of tetracaine are increased over those of procaine by the alteration in structural configuration and by the increase in molecular weight (Ref. 3).

Tetracaine is a teriary amine and, therefore, is a base. It forms salts with various acids including hydrochloric acid. It is generally used in the form of its salts. One gram of the base dissolves in approximately 1,000 mL water. Tetracaine base is much more soluble in organic solvents than water. One gram of the base dissolves in 5 mL alcohol, 2 mL chloroform, and 2 mL ether.

Tetracaine base is less stable than its salts. It is readily soluble in oils and oleaginous bases. The base may be incorporated into water-soluble creams for topical use. It is not as readily released from petrolatum bases when applied topically as it is from water-soluble bases (Ref. 4).

Aqueous solutions of the base decompose rapidly upon standing. Tetracaine hydrochloride occurs as a fine white crystalline odorless powder which has a slightly bitter taste followed by a sense of numbness. Aqueous solutions of the hydrochloride are neutral or slightly acid to litmus. Solutions of the base are alkaline. One part of tetracaine hydrochloride is soluble in 7 parts of water. It is soluble in alcohol but insoluble in ether and benzene. Tetracaine hydrochloride melts between 147° and 150° C (Ref. 1).

Tetracaine salt solutions can be sterilized by boiling for short periods of time. Tetracaine hydrochloride powder or crystals, or aqueous solutions slowly undergo a chemical change and lose their anesthetic potency. The shelf life is limited to less than 1 year. The shelf lives of ointments and other preparations containing the base used topically are not known (Ref. 3).

(1) *Safety.* The Panel concludes that tetracaine is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Although tetracaine base is sparingly soluble in water, sufficient quantities can be absorbed from extensive areas of damaged skin or from the mucous membranes in quantities that produce adverse systemic effects (Ref. 3). High plasma levels of tetracaine will produce convulsions and cardiac depression as do other topical anesthetics of the "caine" type. Adriani and Campbell (Ref. 4) have indicated that the cardiovascular type of reaction may occur without central excitation and cause syncope (fainting) and cardiac arrest. This type of reaction often occurs abruptly without warning and is usually fatal (Ref. 5).

Tetracaine is 10 times more toxic than procaine when administered intravenously in animals. Its relative toxicity is equal to that of procaine since 1 mg is equal to 10 mg procaine in potency and toxicity. Due to its potency, dosages of tetracaine preparations are more difficult to control and over dosage occurs more readily than with less potent drugs. The intraperitoneal $LD_{50}$ of tetracaine in mice is 70 mg/kg. Data on animal toxicity are not in agreement due to different methods of studying toxicity by different investigators. Rapid intravenous injection of tetracaine preparations into animals irrespective of species, causes convulsions and circulatory system depression (Ref. 6). The differences in results obtained by different investigators are merely quantitative. Qualitatively, the responses are the same.

Tetracaine appears to manifest a greater degree of myocardial depression than do other drugs of the "caine" type when the plasma concentrations reach toxic levels (Ref. 5).

Tetracaine is hydrolyzed by pseudocholinesterase in the blood as are procaine and other esters of paraminobenzoic acid. The rate of hydrolysis, however, is approximately one-fifth the rate of procaine (Ref. 3). This slower rate of detoxification contributes to the greater degree of toxicity it manifests compared to other drugs of the "caine" type.

Tetracaine manifests no well-defined chronic toxicity. Adverse reactions from repeated use have not been reported. The action perineurally is reversible, and no histological changes have been demonstrated in nerve tissues. The toxic dose in humans is not known. The maximum limit of dosage of tetracaine hydrochloride perineurally or by infiltation is considered to be between 75 to 100 mg in healthy adults. Topically, on the mucous membranes of the pharynx, the maximum dose is considered to range between 25 to 40 mg (Refs. 3 and 5). Tetracaine manifests no appreciable degree of irritancy when injected or applied topically. Since tetracaine can act as a hapten, it is capable of producing allergic-type reactions mediated by immunoglobulin E (Ref. 3). It may also, after repeated topical applications, cause the cytotoxic type of reaction (Refs. 3 and 5).

Tetracaine base is safe when applied to limited areas of damaged skin. It is also safe when applied to intact skin because absorption and penetration occur slowly. Tetracaine base is readily absorbed from all mucous membranes. High plasma levels may result, causing fatal reactions. The sensitizing potential of tetracaine is no greater than it is with other topical anesthetics. Since tetracaine is a derivative of paraminobenzoic acid, mention is frequently made of possible cross-sensitization with other aminobenzoates, but documentation that this occurs and data substantiating this contention are sparse and not convincing. Cross-sensitization with other derivatives of aminobenzoic acid may occur, but it is rare (Ref. 5).

(2) *Effectiveness.* The Panel concludes that tetracaine is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The un-ionized tetracaine base penetrates and stabilizes the axonal membrane and causes a blockage of the pain and other receptors in the skin. Tetracaine is much more lipid soluble than procaine and has 10 times the protein-binding capacity of procaine (Ref. 3). Tetracaine, therefore, has a longer latent period due to its slower penetration and diffusibility. It is two to four times longer lasting than procaine due to this greater lipid solubility and protein-binding effect. The duration of action is variable, as is the case with other local anesthetics and depends upon the site of application. This variability of duration from one area to another is due, to a great extent, to the differences in vascularity of the tissues. Tetracaine base and tetracaine salts are effective on the mucous membranes when applied topically (Ref. 5).

(3) *Evaluation.* The Panel concludes that tetracaine base is effective topically on the mucous membranes. However, due to the fact that serious and rapidly occurring fatal reactions due to systemic toxicity can occur when used by those not familiar with the hazards, the Panel recommends that it remain a prescription item for oral health care products and not be allowed for use in OTC products.

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(5) OTC Volume 060047.

j. *Tetracaine hydrochloride.* The Panel concludes that tetracaine hydrochloride is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Tetracaine hydrochloride is the salt of the tertiary amine tetracaine which has been described elsewhere in this document. (See part III. paragraph B.2.i. above—Tetracaine). Tetracaine hydrochloride consists of a white crystalline power that is odorless and hygroscopic. Tetracaine hydrochloride is soluble, 1 part in 7 parts of water, unlike

the base which is poorly water soluble. Tetracaine hydrochloride has a slightly bitter taste followed by a sense of numbness. Tetracaine hydrochloride melts between 147° and 150° C (Refs. 1 and 2).

Tetracaine hydrochloride hydrolyzes slowly and loses its anesthetic activity with time. The shelf-life of the powder in sealed ampulses is less than 1 year. The hydrochloride is the most widely used salt. Solutions of the hydrochloride salt are more stable than the base. The hydrochloride is converted to the base when injected or applied topically to the mucous membranes by the buffering mechanisms of the tissues, and for this reason the drug penetrates very rapidly into the blood stream (Refs. 3 and 4).

(1) *Safety.* The Panel concludes that tetracaine hydrochloride is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Tetracaine hydrochloride is 10 times more potent and toxic than procaine (Ref. 1). It may be absorbed in large quantities from abraded and denuded areas since it is very water soluble. Tetracaine hydrochloride produces convulsions and cardiac depression similar to other local anesthetics (Ref. 5). Reactions of this type from topical application of tetracaine hydrochloride to the mucous membranes have been reported. Tetracaine hydrochloride manifests no appreciable degree of irritancy. The sensitizing potential is low, but, like all other anesthetics of its type, will cause allergic reactions. Tetracaine hydrochloride can act as a hapten and cause allergic reactions mediated by IgE immunoglobulins (Ref. 6). Repeated application can cause the cytotoxic type of sensitization mediated by the T-cell lymphocyte. Local reactions are characterized by rashes, aczema, etc. (Ref. 7).

(2) *Effectiveness.* The Panel concludes that tetracaine hydrochloride is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Tetracaine hydrochloride is highly ionized and does not readily penetrate lipid barriers of the cell membrane. Tetracaine hydrochloride is very slowly absorbed from the intact skin and, therefore, exerts no significant therapeutic effect (Refs. 4 and 8). Aqueous solutions are acidic (pH 5 to 6), but when injected into tissues or applied topically on the mucous membranes they are converted to the base, which is the physiologically active form. Tetracaine hydrochloride is effective when it comes into contact with the tissue fluids because it is converted to the base, the active form, penetrating the neuronal membrane and blocking conduction of nervous impulses.

(3) *Evaluation.* The Panel concludes that tetracaine hydrochloride is effective as a topical anesthetic/analgesic on the mucous membranes. Due to its potential for producing severe, obvious, and often fatal systemic reactions, however, it is not recommended for use in OTC products but should remain available by prescription.

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**Category II Labeling (Anesthetics/Analgesics)**

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use, or for description of product attributes for products containing anesthetic/analgesic active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action when it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Relieves dryness."

(2) "First aid for throat irritations."

(3) "Soothing to smokers throat."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms, that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Is quick comfort to irritated throats."

(2) "Fast acting local anesthetic action."

(3) Fast acting temporary relief of minor throat pain."

(4) "Fast temporary relief of minor sore throat pain."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Superior and fast acting relief of minor throat pain, cough, or colds."

(2) Adding such terms or "plus" etc.

d. *Statements or phrases that are vague in this meaning and cannot be readily understood or are misleading.* (1) "Soothes tired throats."

(2) "Is quick to comfort irritated throats."

(3) "For temporary relief of sore throat associated with colds and excessive smoking."

(4) "Promotes healing by protecting the affected area from further irritation (oral bandage)."

(5) "Clings tenaciously to oral tissue."

e. *Statements or phrases in the indications for uses that state or imply that the product is to be used to treat a disease process or lesion, the diagnosis of which must be made by a physician.* (1) "For temporary relief of pain associated with tonsillitis and pharyngitis."

(2) "For temporary relief of pain associated with canker sores."

(3) "Temporary relief of pain of stomatitis."

(4) "Relief of pain and discomfort in pharyngitis and throat infections."

(5) "Relieve minor throat pain and pain from aphthous ulcers (canker sores)."

(6) "For acute tonsillitis."

f. *Statements, phrases, or terms in the indications for use that describe the pharmacologic effect or class of a drug or type of formulation containing the ingredients instead of designating the symptoms which the product is intended to relieve.* (1) "Anesthetic."

(2) "Analgesic."

(3) "Liquid anesthetic for mouth and throat."

(4) "As a topical anesthetic."

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

**Category III Active Ingredients**

Eucalyptol
Methyl Salicylate
Thymol

a. *Eucalyptol.* The Panel concludes that eucalyptol is safe but that there are insufficient data available to permit

final classification of its effectiveness as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Eucalyptol is a volatile oil prepared by steam distillation of the fresh leaves of *Eucalyptus globulus* (Ref. 1). The eucalyptus tree is native to Australia, Tasmania, and the Malysian regions.

Eucalyptol is colorless, or a pale yellow volatile liquid with a characteristic aromatic, somewhat camphoraceous odor, and a spicy and cooling taste (Ref. 2). Its specific gravity is 0.905 and its refractive index is 1.458 to 1.470. Approximately 70 percent of eucalyptus oil is in the form of one of its active ingredients, namely, eucalyptol (Ref. 3). Eucalyptol is also known as cineol, cineolcayeptol, and cajuptol. It is insoluble in water, but it is miscible with alcohol, chloroform, and ether. Eucalyptus oil and eucalyptol have both been characterized as flavors in the "National Formulary." They both have feeble analgesic and antiseptic effects and both have been used as stimulatory expectorants and as vermifuges (Refs. 4 and 5).

The characteristic odor of eucalyptol is considered to be a "medicinal odor" by the users of OTC products, and it acts as a placebo. Eucalyptol has been used topically for the treatment of certain forms of skin diseases. It is an active germicide, but is not as effective as many other volatile oils (Ref. 2).

(1) *Safety.* The Panel concludes that eucalyptol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

If eucalyptol is taken internally in large quantities, toxic symptoms may occur. These symptoms include epigastric burning, nausea, vomiting, tachycardia, dizziness, muscular weakness, a feeling of suffocation, and in severe cases delirium and convulsions. Death has occurred in about one-third of the human subjects who ingested between 10 and 30 mL of the oil. Idiosyncrasy towards small doses may be manifested by skin eruptions (Refs. 6, 7, and 8). Sensitization to eucalyptol has been observed but is believed to occur infrequently (Refs. 6, 9, 10, and 11).

Jenner et al. (Ref. 12) found that the $LD_{50}$ of eucalyptol for rats is 250 mg/kg. It is relatively safe when applied topically to the skin. Jori and Briatico (Ref. 13) studied the effects of administering eucalyptol subcutaneously to pregnant rats. It was noted that eucalyptus oil greatly increased the liver microsomal activity during and after pregnancy. It was also found that this increased activity was higher in the fetal and newborn offspring.

The question of carcinogenic activity of eucalyptol has been raised by several investigators (Refs. 14 and 15). Homburger (Ref. 15) found that eucalyptol applied to the skin of mice caused development of tumors in about 10 percent of the animals treated.

Marketing experience of a topical anesthetic product containing small amounts of eucalyptol produced no evidence of lack of safety (Refs. 16 and 17).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of eucalyptol as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Historically, eucalyptus oil has been used as a stimulating expectorant and as a locally applied antiseptic with a very mild anesthetic effect. It has also been used as a vermifuge. Eucalyptol is a mild local irritant that is used as an inhalant, especially in bronchitis. It can be administered by inhalation by adding a teaspoonful to hot water and vaporizing the water. It can be given internally by placing 5 to 10 drops on sugar. Eucalyptol is used in the treatment of the "common cold"; sprays of 3 to 5 percent solutions in liquid petrolatum have been used. The usual dose is 0.3 mL.

The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products in the **Federal Register** of September 9, 1976 (41 FR 38347) has written a great deal on the antitussive effects of eucalyptol in various currently marketed OTC topically applied preparations consisting of ointments, liquids, and tablets. The conclusions of this Panel support the conclusions discussed above; namely, eucalyptol has no analgesic effect and does not interfere with the reflex arc involved in completion of the cough reflex resulting from local stimulus in the pharynx. The data submitted consisted of combinations of volatile oils that included eucalyptol as one of the ingredients. Data were submitted concerning the effectiveness of the ingredient alone.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.025- to 0.1-percent concentration of eucalyptol in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 1 to 30 mg of eucalyptol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care anesthetics/analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

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(16) OTC Volume 060013.

(17) OTC Volume 060014.

b. *Methyl salicylate.* The Panel concludes that methyl salicylate is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Methyl salicylate is the methyl ester of salicylic acid which is made by esterifying methyl alcohol with salicylic acid. One milliliter methyl salicylate has a salicylate content equivalent to 1.4 g aspirin. Methyl salicylate is a volatile liquid having a density of 1.18 g/mL. At low concentrations, it is employed as an organoleptic agent for both its condimental flavor and pleasing aroma. Methyl salicylate has a counterirritant action for temporary relief of deep-seated pain when applied to the skin (Refs. 1 through 5).

Methyl salicylate penetrates the intact skin and is absorbed into the system circulation. It is also readily absorbed from the mucous membranes. Some data are available indicating that the amounts absorbed percutaneously are sufficient to have significant anesthetic activity (Refs. 6 through 9). Methyl salicylate has been used on the mucous membranes to obtain systemic effects. There are no data to substantiate that methyl salicylate blocks nerve conduction as do topical anesthetics, such as benzocaine.

Prior to the discovery of a method for chemical synthesis of methyl salicylate, it was produced by steam distillation from natural sources. The natural-source products are known as gaultheria oil, betula oil, sweet birch oil, teaberry oil, and wintergreen oil. Today, these names are used synonymously with methyl salicylate. Methyl salicylate is prepared synthetically by esterifying salicylic acid with methanol.

(1) *Safety.* The Panel concludes that methyl salicylate is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has given much consideration to the question of toxicity of methyl salicylate. The association of the odor of methyl salicylate with the odor of candy (wintergreen and teaberry flavors) has been linked by the American Medical Association to the ingestion by children of drug products containing more than therapeutic and safe amounts of methyl salicylate (Ref. 10). However, the National Clearing House of Poison Control Centers, Bethesda, Maryland, reviewed reports of poisoning due to ingestion of methyl salicylate, primarily in ointment formulations, which revealed no deaths and few cases with severe symptoms from 1970 to 1972. Recent regulations requiring the use of child-resistant containers for liquid preparations containing more than 5 percent methyl salicylate (16 CFR 1700.14(a)(3)) provide an important safeguard for small children, who have constituted a large percentage of the victims of accidental poisoning from drinking poisonous substances.

Except for severe local irritations of the mucous membranes, ingested methyl salicylate is not notably different in its toxic actions from other salicylates. Metabolic acidosis may be a more prominent complication of salicylate overdosage with the methyl ester than with other derivatives of salicylic acid (Ref. 11). The average lethal dose of methyl salicylate is approximately 10 mL for children and 30 mL for adults (Refs. 12 and 13). However, the ingestion of as little as 4 mL (4.7 g) methyl salicylate has caused fatalities in children (Ref. 14). For comparative purposes, it should be noted that the salicylate content of 4 mL (4.7 g) methyl salicylate is equivalent to 4.3 g salicylic acid, 4.96 g sodium salicylate, or 5.6 g aspirin. Death has ensued following ingestion of 3 g salicylic acid and 4 g sodium salicylate (Ref. 15). The toxic dose of aspirin is in the range of 75 to 150 mg/kg. This is equivalent to 5.3 to 10.5 g for a 154-lb adult. Methyl salicylate is generally recognized as safe (GRAS) in candy at 0.03 percent and GRAS in chewing gum at 0.33 percent.

There is adequate evidence to support the contention that ingestion of more than small condimental amounts of methyl salicylate is hazardous. However, the concentrations of methyl salicylate contained in marketed oral health care products reviewed by the Panel are within a range which the Panel considers safe for OTC use on the mucous membranes of the mouth and throat. The Panel does recommend, in the interest of safety, that a maximum concentration of 0.4 percent be used.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of methyl salicylate as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The amount of salicylate absorbed following topical application of methyl salicylate is unpredictable. There are insufficient data to support the contention that salicylates stabilize the neuronal membrane as do topical anesthetics such as benzocaine or tetracaine. Conclusions that it is an anesthetic have been based largely upon the assumption that blood levels of topically administered salicylates must be of the same order as "effective blood levels" associated with orally administered salicylates. Lim and co-workers (Ref. 16) have observed that salicylates elicit their anesthetic effects peripherally, not centrally, and block pain by direct action on pain receptors by inducing an anti-inflammatory action. Recent advances in knowledge regarding the supposed role of prostaglandins causing pain syndromes and the ability of salicylates to inhibit the biosynthesis of prostaglandins may shed further light upon the role of salicylates applied topically to relieve locally painful symptoms. It has not been established that methyl salicylate applied to the mucous membranes plays any such role.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use up to a 0.4-percent concentration of methyl salicylate in the form of a rinse, mouthwash, gargle, or spray, not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care anesthetics/analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

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c. *Thymol.* The Panel concludes that thymol is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol, also known as thyme camphor, is 5-methyl-2-isopropyl-1-phenol. It may be prepared synthetically or obtained from volatile oils distilled from *Thymus vulgaris* and other related plant sources. Thymol occurs as colorless crystals which are often large, or as a white crystalline powder. It melts at 51° C and boils at 233° C. One gram dissolves in 1 liter (L) of water. It is highly soluble in alcohol, chloroform, and in mineral and other volatile oils (Ref. 1). Thymol has a characteristic aromatic thyme-like odor and a pungent taste. It has appreciable volatility and can be administered with steam or in water vapor when prepared in an aqueous solution. Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal, and anthelmintic properties (Ref. 2). Its antimicrobial effects have been described elsewhere in this document. (See part IV. paragraph B.3.w. below—Thymol.)

(1) *Safety.* The Panel concludes that thymol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol has a pleasant, aromatic odor. It is sometimes referred to as a volatile or essential oil. Thymol has been used for a variety of medicinal purposes but has, in many cases, fallen into disuse and been supplanted by newer, more effective drugs. It has been incorporated into mouthwashes for its antiseptic action and as a flavorant. Thymol has been used topically and orally as an antifungal agent for the treatment of actinomycosis. It also has been used internally as an intestinal antiseptic and anthelmintic, especially against hookworm (Refs. 3 and 4).

The intravenous $LD_{50}$ of thymol in mice is 74 mg/kg (Ref. 5). Jenner (Ref. 6) studied the acute oral toxicity of thymol instilled into the stomach by intubation in the rat and guinea pig. The $LD_{50}$ for the rat was 980 mg/kg and for the guinea pig, 880 mg/kg.

Chronic toxicity was observed in 5 male and 4 female rats given an oral dose of 10,000 parts per million for 19 weeks. No untoward effects were noted after this period of time (Ref. 7).

Oral ingestion of 1 g thymol usually does not cause any adverse symptoms except the feeling of warmth in the stomach. According to Sollman (Ref. 4):

> Larger doses [than 1 g] produce dizziness, severe epigastric pain, excitement, soon followed by nausea, vomiting, marked weakness, drowsiness, quick soft pulse, tinnitus and deafness, salivation, sweating; then collapse with cyanosis, fainting, coma, low temperature, slowed pulse and respiration. Abortion may result. Rashes are not uncommon.

A report by Barnes (Ref. 8) noted that over 1,000,000 doses of thymol averaging 1 g per dose resulted in reported deaths of 20 debilitated patients.

Samitz and Shmunes (Ref. 9) noted that dentists and other allied personnel found thymol one of the less frequent sensitizers in occupational dermatoses. Thymol irritates the mucous membranes, but when topically applied to the skin it has little effect and is virtually unabsorbed (Ref. 4). The oral toxicity of thymol is about one-fourth that of phenol and, if it is absorbed, one-half is metabolized totally. The remainder is conjugated with sulfuric acid and glucuronic acid and excreted into the urine (Ref. 4).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of thymol as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol was first introduced as a disinfectant. It has a phenol coefficient of 27.6, but its activity is greatly reduced by the presence of proteins. It also has some antiviral activity (Ref. 10). In 1891 Potter (Ref. 11) stated that thymol was a topical anesthetic when used on the skin and mucous membranes. Buckley (Ref. 12) also noted that thymol had topical analgesic properties and was considered superior to phenol as an antiseptic.

The Panel concedes that it is possible that thymol is an anesthetic when topically used on the mucous membranes of the oral cavity because of its phenolic nature, but it does not have sufficient evidence and documentation supporting this claim. Most of the literature reveiwed on the subject refers to thymol's antimicrobial and antifungal effects. Although 1 to 2 percent concentrations of thymol have been used clinically for topical analgesia, there is insufficient evidence as to the effectiveness of such concentrations.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.006- to 0.1-percent concentration of thymol in the form of rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 0.2 to 15.0 mg of thymol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervison of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/

analgesic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evalution.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care anesthetic/analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

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**Category III Labeling**

None.

### *C. Data Required for Evaluation*

The Panel agrees that the protocols recommended in this document for studies required to bring a Category III drug into Category I are in keeping with the present state of the sciences of pharmacology and therapeutics and the art of medicine and do not preclude the use of any advancements or improvements in methods for obtaining data that might be developed in the future.

1. *General principles in the design of an experimental protocol for testing topical anesthetics/analgesics for use in the oral cavity.* The effectiveness of topical anesthetics/analgesics should be determined by their ability to obtund or relieve the pain and discomfort due to acute or chronic pathologic states of the mouth and throat. The Panel recognizes that there are no established protocols for testing the effectiveness of this category of product by using objective methods and that all testing is, by and large, subjective. Tests can be made on patients who have pain or on volunteers in whom pain can be induced experimentally. All tests should involve a double-blind, placebo-controlled assessment of the ability of the drug to decrease pain due to sore mouth and sore throat.

The data should be obtained using the same drug that is present in the OTC preparation. It should be used in the same dosage and applied in the same manner recommended in the instructions in the labeling of the preparation. Since anesthetics/analgesics may be administered repeatedly during episodes of pain, dosing should be at appropriate times necessary to maintain optimal relief of symptoms. Data should also be obtained by testing the topical anesthetics/analgesics in recommended concentrations and at maximal dosage frequencies for periods of at least 5 days. This must be done in order to assess both its sustained effect and the potential for inducing irritancy or allergenicity.

Volunteers without pain may be tested using an established method of algesimetry such as that of Adriani and Zepernick (Ref. 1) which utilizes an electrical current applied to the tip of the tongue as a painful stimulus. Nebulized solutions of citric acid may also be used, particularly when obtaining data substantiating a cough claim.

2. *Selection of patients.* Selection of patients for testing should be based on the cause and established diagnosis of sore mouth or sore throat. Patients with chronic conditions causing sore mouth or sore throat usually present relatively stable conditions; consequently, subjects of this type may be selected for a cross-over, double-blind study. Such subjects can serve as their own controls. Subjects without pain being tested using algesimetric methods of assessment may be tested in this manner also. Patients with acute infections, or conditions that induce pain in the mouth and throat represent a larger portion of a patient type to self-medicate with a topical anesthetics/analgesics. Because of the relatively brief duration of these acute disorders and greater variation in type and intensity of the pain or discomfort and stability of the lesion causing the pain, a greater number of patients should be studied than when the cross-over, double-blind technique is used. They should be studied by assigning them in random fashion into two groups, a placebo group and a drug group. The placebo should be indistinguishable from the drug being tested. Each should be of equal size. Further, for comparative purposes, all groups must be matched by age, sex, and, if possible with the exception of the volunteers, the degree of pain at the time of the study.

3. *Methods of study.* Observations should include subjective response on patients with pain and the responses measuring the anesthetic/analgesic effect by a technique of algesimetry. The technique employed by Adriani and Zepernick (Ref. 1) described above, using electrical current applied to the tongue is acceptable to the Panel and has been widely used in evaluations of effectiveness of topical anesthetics/analgesics on the mucous membranes. Individual patient diaries should be kept in which is recorded all pertinent data such as date, times of testing, onset and duration of pain relief, dose, etc. Observation should include the time of onset, magnitude, and duration of the response. A scoring technique evaluating the effectiveness of the drug in relieving pain, such as indicating the response as 0 for no effect, 1 for poor, 2 for fair, 3 for good, and 4 for excellent can be used.

4. *Interpretation of the data.* The recommended dose for the test drug should induce a statistically significant reduction in mouth and throat pain when compared with a placebo response.

Evidence of a drug's effectiveness is required from 25 subjects with chronic pain and 25 volunteers. Subjects should be from a target population for whom the drug is intended to be used. Studies involving patients with acute pathologic states for whom no baseline can be obtained should include 75 to 100 subjects. A minimum of three different investigators or laboratories must be used.

All data submitted to the FDA must present both favorable and unfavorable results.

5. *Evaluation of safety.* Tests of safety should involve usual tests for acute and chronic toxicity relative to the known possible adverse effects of drugs described previously. (See part II. paragraph C.2. above—Testing for recategorization of Category III

ingredients.) Tests should be done and dose response curves be established for acute toxic effects utilizing the dose range from minimum effectiveness dose up to a maximum therapeutic effectiveness.

**Reference**

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## IV. Antimicrobial Agents

### *A. General Discussion*

The Panel disagreed on important issues relevant to the safety and effectiveness of antimicrobial agents and also on the types of testing methodologies to be included in the data required for evaluation of antimicrobial agents. Accordingly part IV.—Antimicrobial Agents consists of a majority report and a minority report. The minority report reflects the opinion of one Panel member.

1. *General comments.* Topical antimicrobial ingredients are applied to the mucous membranes of the mouth and throat to kill, inhibit the proliferation of, or alter the metabolic activity of all types of microorganisms, both pathogenic and non-pathogenic. This process is called "antiseptics"; agents that are used for this purpose are called "antisepsis." The term "antiseptic" implies that some therapeutic benefit results when such agents are used. Antiseptics are used in an attempt to sterilize intact cutaneous and mucous surfaces, contaminated or infected wounds, mucosal ulcerations, or other lesions caused by pathogenic microbial activity. There is considerable evidence indicating that these agents are not only ineffective but may also retard the healing of clean or infected wounds.

There is an abundance of documentation, both in older and more recent authoritative texts written by authorities on microbiology, which states that the topical application of antiseptics is of doubtful therapeutic value.

Grollman and Slaughter (Ref. 1) states as follows:

A very large number of substances possess disinfectant properties, that is, are capable of destroying microbes when they can be applied in sufficient quantity. They have no specific action on the microbes, however, but act as general protoplasmic poisons, destroying living tissue of all kinds wherever they come in contact with it. On the other hand, drugs such as strychnine, which act on specialized parts of the vertebrate organism and have less effect on the less differentiated tissues, are equally harmless to the undifferentiated protoplasm of the microbes. It is of importance to note that the ordinary antiseptics do not act more strongly on microbes than on the tissues in which they are embedded or on the phagocytes with which the organism is combating the infection. The destruction of the septic organisms in a wounded surface entails the destruction of the surrounding cells also. Thus disinfection can only be carried out in a part in which the superficial cells are not of vital importance and may be restored by new growth. It is therefore impossible to disinfect the tissues of the body as a whole unless a drug is parasitotropic, that is, has a specific affinity for the parasite rather than for the organs in general (organotropic). Although many attempts were made to find drugs manifesting such selectivity it was only with the introduction of the sulfonamides, antibiotics and other systemic anti-infectives that this goal was attained. By the local or systemic application of these substances antisepsis may be obtained without injury to the normal tissues. The term antiseptic is now usually limited to the drugs exerting a local anti-infective action although in its broad sense it should also include the systemic anti-infectives described in previous sections.

* * * If microbes were confined to the surface, the latter would be sufficient for their destruction, but in order to disinfect a wound it is necessary to penetrate more deeply and thus efficient disinfection implies a certain amount of destruction to the tissues in which the microbes are harbored. This local destruction of cells and nervous structures induces pain and irritation and many efficient disinfectants are irritants. There action as irritants arises from the same qualities as their disinfectant power, namely, from their general toxicity to living matter.

When a surface has been poisoned by means of disinfectants, it heals less quickly, and this had led to the more sparing use of antiseptics and to the development of the aseptic method, in which organisms are excluded instead of being admitted and then destroyed. With the discovery of the sulfonamides and antibiotics these, in turn, displaced the previously used antiseptics in many cases for these substances not only inhibit the growth of the invading pathogens but induce only minimal or no injury to the normal tissues.

In addition to their local effect, many of the antiseptic and disinfectant drugs have a further poisonous action when they are absorbed and circulate in the blood, and this has led to a further limitation of their use. This general action does not necessarily arise from the qualities which render them antiseptic, and may be avoided by care in the choice of the drug and in its use.

Sollmann (Ref. 2) states as follows:

The field of antiseptics has become considerably restricted since they were introduced by Lister. They can be highly effective outside the body but they rarely penetrate sufficiently to kill bacteria in living tissues. When they do penetrate they are generally more effective in killing tissue cells than the bacteria. They do not really disinfect the tissues but may kill and embalm the bacteria on the surface.

Goth (Ref. 3) states as follows:

Prior to the discovery of chemotherapeutic agents, there was much preoccupation in synthesizing new compounds that could kill bacteria rapidly in high dilutions. The new antiseptics were generally compared with phenol and the ratio of the dilution that was necessary for killing test organisms in vitro was called the phenol coefficient. These efforts were so successful that antiseptics were synthesized that were 100 times more potent than phenol in killing bacteria in less than 10 minutes.

In retrospect much of this effort was misdirected. Any drug that can kill bacteria in a few minutes is bound to have a toxic effect on mammalian tissues. It is not surprising that even the most potent antiseptics were completely incapable of curing a systemic bacterial infection because the testing methods used for their development were designed for potency and not a favorable therapeutic effect. The discoverers of Prontonsil decided to test every compound against systemic infection in mice. The sulphonamides and penicillin would never have been discovered by testing methods, such as the use of the phenol coefficient. Not only the phenol coefficient but all the tools for evaluation of antiseptics are poor. It is not surprising that the field is dominated by empiricism and is greatly influenced by fashion.

Esplin (Ref. 4) states:

No group of drugs is employed more widely than the antiseptics and disinfectants. Among the agents discussed in this chapter are those germicides that are the most useful; however, some agents are mentioned not because they are particularly efficacious but because they are widely used.

The concept that infectious diseases are spread by microorganisms, at first so reluctantly accepted by the medical profession, is now embraced by the layman with an enthusiasm that is exceeded in degree only by ignorance. Each decade has seen advances in the discriminate and scientific use of disinfectants in reducing dissemination of pathogenic microorganisms and in the control of systemic and local infections by antibiotics and antiseptics. Nevertheless, the layman frequently employs the readily available germicidal agents in a ritual manner that rarely produces substantial benefit and often results in serious harm.

But the layman does not acquire this ritual instinctively nor does he follow it without persuasion. Those who profit from the promotion of germicidal preparations use the most advanced technics in the advertising media to induce the uniformed to purchase, through fear of infection, preparations that are usually costly, often worthless, and sometimes dangerous. The insecure layman is offered germicidal solutions, sprays, powders, and ointments for application to every surface and orifice of the body. The germophobia that drives him to this needless expense is entirely inappropriate to the present age. Information more directly serving the interests of public health would instruct in the rational prevention and

treatment of infectious disease. This "information gap" is illustrated by the common practice of using ineffective antiseptics in wounds, cuts, and abrasions in the mistaken belief that they reduce the chance of acquiring tetanus, a disease that is entirely preventable by proper immunization.

Nevertheless, there are indispensable uses of disinfectants in the household, in hospital sanitation, and in public health measures. Likewise, antiseptics find many legitimate therapeutic applications. The extent of use of antiseptics in therapy of local infections has declined with the increasing number of antibiotics and other systemic chemotherapeutic agents available. In spite of this fact, antiseptics are sometimes still of value in treating local infections caused by microorganisms refractory to systemic chemotherapy. It is the problem of the physician to choose wisely from the vast number of available drugs and to delineate the beneficial and the harmful uses of germicides.

Esplin (Ref. 4) further states as follows:

* * * Among the first uses of antiseptics in medicine were the treatment of wounds. It is now apparent that most germicides are of little value for this purpose due to their poor penetration into foci of infection, relatively low efficacy in body fluids, and their propensity for causing local tissue damage. They cannot be relied upon to prevent infection from bacterial contaminants, and they are, in general, markedly inferior to systemic chemotherapeutic agents in controlling an infection once it has developed. In the hands of experienced surgeons, selected germicides may be useful in cleansing wounds and in reducing bacterial contamination. However, the common belief that the substantial benefit is obtained from the application of antiseptics to wounds, cuts, and abrasions is not supported by the considerable evidence in this field. The various applications of surgical antiseptics have been considered in detail by Price (1968). [Price, P. B., "Surgical Antiseptics," *in* "Disinfection, Sterilization, and Preservation," edited by C. A. Lawrence and S. S. Block, Lea and Febiger, Philadelphia, pp. 401–429, 1968.]

The majority of local infections respond more dramatically to appropriate chemotherapeutic drugs administered systemically than to antiseptics. Antiseptics are sometimes useful in treating infections caused by microorganisms that are unaffected by chemotherapeutic drugs, through the development of drug resistance or otherwise. In refractory infections, antiseptics are occasionally employed in conjunction with systemic chemotherapeutic agents. Furthermore, germicidal drugs are useful in the prophylaxis against specific infections.

Jawetz, Melnick, and Adelberg (Ref. 5) state as follows:

*Disinfectants.* Disinfectants and antiseptics differ from systemic reactive antimicrobials in that they possess little selective toxicity. They are toxic not only for microbial parasites but for host cells as well; therefore, they can be used only to inactivate microorganisms in the inanimate environment or to a limited extent on skin surfaces but they cannot be administered systemically and are not active in tissues.

Modell, Schild, and Wilson (Ref. 6) state as follows:

The number of disinfectants and antiseptics used is large because there is no such thing as an ideal disinfectant. The properties required vary widely, according to the manner in which the drug is intended to be used. The intensity and speed with which a drug kills bacteria can be measured in a test tube, and this information is of great value for determining, for example, the relative efficiency of disinfectants when applied to inorganic material. Such measurements give little indication of the relative values of disinfectants when applied to living tissues, because in this case the important issue is whether the substance that will kill or at least prevent the multiplication of bacteria will not also injure the surrounding tissues. Indeed, some of the best antiseptics for the treatment of wounds are substances which have a relatively feeble and slow action in vitro, and there are authoritative opinions that beyond their mechanical effects of removing debris and soil they accomplish little.

Banovetz (Ref. 7) states:

*Topical Medication for the Throat.* Definitive topical treatment of pharyngeal disease is not possible except in monilial infections for which nystatin is used. For the most part treatment is symptomatic. Patients feeling better will continue treatment but the critical physician must regard this as art, and not science. Painting sore throats with 2% silver nitrate or Mandel's solution (iodine) is comforting but not antibacterial.

Medical troches do not deliver drugs below the epithelial surfaces but they may have some surface cleansing action.

Although silver nitrate is not an ingredient considered by the Panel for OTC use, it is a topical antiseptic. Iodine has been considered by this Panel for topical use to treat sore throat and sore mouth.

Harvey (Ref. 8) states:

Antiseptics and disinfectants are employed very widely and are thus deserving of sober consideration.

Once the germ theory of disease was accepted by the medical profession and antisepsis by chemical agents was demonstrated scientifically, topical antimicrobial drugs were employed with naive enthusiasm by both physicians and laymen. Astute physicians early learned the limitations of antiseptics, but the vast majority of physicians and laymen alike employed such drugs uncritically and often inappropriately, encouraged by promotional propaganda almost from the very beginning. Although several effective and useful antiseptics, such as iodine, were known quite early, in the first half of this century there was a rush to accept a host of lesser and even useless drugs. The euphoria surrounding the discovery of the sulfonamides and antibiotics obscured the need for a thoroughgoing appraisal of the value of antiseptics, collectively and individually. Only a few of the antiseptics have been subjected to controlled clinical comparison with other agents, and clinical standards have yet to be accepted. Both laymen and many physicians still continue to employ the topical antimicrobial drugs in a ritual manner that is often irrational, usually ineffective, and occasionally harmful.

Nevertheless, there are indispensable uses of disinfectants in the household, in hospital sanitation, and in public health measures. Likewise, antiseptics find many legitimate therapeutic applications. Even though systemic antimicrobial drugs have quite properly caused a decline in the use of topical anti-infective agents, antiseptics are sometimes still of value in treating local infections caused by microorganisms refractory to systemic chemotherapy and in the supplementation of such therapy. It is the problem of the physician to choose wisely from the vast number of available drugs and to delineate the beneficial and the harmful uses of germicides.

In this chapter [of "The Pharmacological Basis of Therapeutics"], a drug may receive special attention because of its undoubted efficacy, its toxicity, or the need to deflate an undeserved status.

Sanders and Sanders (Ref. 9) state as follows:

Antibacterial agents may adversely affect the host either directly or indirectly. Direct injury, or toxicity, is the focal point of this review. Indirect injury may result from (a) induction of an allergic or hypersensitivity reaction in which components of the immune system (antibody, activated cells, complement) mediate damage to host tissues or (b) alteration of the ecological balance of the normal microbial flora which facilitates superinfection or impairs epithelial physiology or nutrition.

Many clinicians consider the application of antiseptic solutions to contaminated wounds, ulcerations, or other lesions due to, microbial activity an unphysiologic procedure of doubtful value, and they feel that their use can be harmful. Therefore, they recommended that antiseptics not be applied to clean wounds or lesions resulting from microbial activity. Careful cleansing or irrigation of wounds and ulcerations and removal of foreign material from ulcerated surfaces by mechanical means, such as swabbing, irrigation, or use of sprays to assure free drainage, are considered more effective and less likely to injure tissues.

Most antiseptics harm both the microorganism and cells of the host. They cannot be used systemically. Except for use on the skin, they are of limited value. The introduction of anti-infective drugs such as the chemotherapeutic agents, antibiotics,

and other drugs possessing selective toxicity for particular microorganisms or classes of pathogenic microorganisms without harming the cells of the host, has caused relegation of most antiseptics for use in the mouth and throat into obsolescense. It is the consensus of the Panel that the term "oral antiseptic" not be used.

Despite these well-known concepts concerning the possible adverse effects of antiseptic agents, the practice of using these agents to attempt to relieve symptoms due to infections or to accelerate wound healing is so ingrained in the minds of both consumers and health professionals alike that attempting to discourage their use appears to be futile. In addition, the promotional practices of manufacturers of OTC products encourage rather than discourage self-medication with these products.

The ideal antiseptic should destroy all types of bacteria, fungi, viruses, and other infective organisms without harming the living tissues of the host. None, however, have been demonstrated to have this attribute, and some healthy cells are invariably injured. All effective antiseptics are general protoplasmic poisons and most have limited and varying spectra of antimicrobial activity which also limit their usefulness.

Antiseptics and antisepsis must be distinguished from disinfectants and disinfection. Disinfectants are used on inanimate objects to destroy microorganisms that are in the nonsporing state. Some disinfectants, such as phenol and the quaternary nitrogenous compounds, can be used as antiseptics if they can be diluted sufficiently to minimize injury to living tissues without loss of antimicrobial activity. Other antimicrobial agents are not suitable as antiseptics, particularly in the mouth and throat. They may require prolonged contact to be effective and this is usually difficult to achieve on oral mucosa. Futhermore, prolonged contact increases the likelihood of simultaneous injury to the pathogenic organisms as well as to the cells of the host. Sterilization is the complete and total destruction of all microbial life, including bacterial spores, vegetating bacteria, viruses, and fungi. Any agent that does not cause total destruction of microorganisms is a disinfectant when used on an inanimate object and an antiseptic when used on living tissues. The term "sanitize" is used to denote the reduction of bacterial flora on inanimate objects to an acceptable level that reduces the chance of infections. These terms are often confused, used erroneously, and sometimes interchangeably.

In summary, an "antimicrobial agent" kills or interferes with the proliferation and activity of many microorganisms, both pathogenic or non-pathogenic. A therapeutic benefit may or may not be derived from its use. An "antiseptic" is an antimicrobial agent which, when used on living tissues, produces some therapeutic benefit and acts to counteract an infection. A "disinfectant" is an antimicrobial agent used on inanimate objects to kill all types of microorganisms that are in the nonsporing state. A "sanitizing agent" is an antimicrobial agent that reduces bacterial flora on inanimate objects to a level that reduces the possibility of infections.

The virucidal effects of many antimicrobial agents have not been established with certainty. Many agents that kill bacteria, fungi, or other pathogenic organisms do not kill viruses.

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2. *Antimicrobial agents for use in the oral cavity.* The most widely used antimicrobal agents in OTC oral health care drug products are aliphatic alcohols, aromatic alcohols (phenolic compounds), elemental and organic iodine preparations, organic derivatives of mercury, preparations containing aluminum, zinc, or chromium, cationic agents such as quaternary nitrogenous compounds, anionic agents such as detergents and soaps, boric acid and other boron derivatives, chelating agents such as oxyquinoline, and oxidizing agents such as the peroxides. Various balsams, tars, and aromatic bodies, often referred to as volatile (essential) oils, have been used as antimicrobial agents since earliest antiquity. A general discussion of the chemical nature and therapeutic effectiveness of these agents appears below.

The ideal antimicrobial agent should possess selective toxicity, that is, it should kill or permanently inhibit the activity of pathogenic organisms without causing injury to the cells of the host harboring the pathogen. None of the antimicrobial agents used in OTC oral health care products have been demonstrated to possess this attribute. The antibiotics and various chemotherapeutic agents come closest to attaining this attribute. These, however, are not available to consumers as OTC products because the diagnosis of the clinical conditions requiring their use, determination of appropriate dosage, and the selection of the proper antimicrobial agent must be done by a dentist or physician. Furthermore, they act systemically and must be administered orally or parenterally so that they can circulate in the blood and reach the infected areas via that route.

It is the consensus of the Panel that the effective use of antimicrobial agents in OTC products for self-medication and relief of symptoms due to infections of the mouth and throat caused by pathogenic organisms has not been convincingly demonstrated. The use of these antimicrobial active ingredients appears to be unwarranted, and there is evidence that they may be harmful in some instances. The Panel recognizes that antiseptics have widespread acceptance by the lay consumer even though indisputable evidence of their effectiveness has not been documented by controlled studies or proven to be of benefit from widespread clinical experience. The Panel, therefore, feels obligated to discourage the use of antimicrobial agents in oral health care products and recommends only those that are proven to be safe and effective and can be used properly for self-medication.

The Panel concludes that there are a number of valid reasons for advocating that antimicrobial agents not be used for therapeutic purposes in OTC oral health

care preparations. First, the Panel believes that the consumer is unable to determine the identity of organisms causing the symptoms requiring treatment and would not be able to exercise proper judgement in selecting the correct agent, even if the nature of the microorganism were known. Second, topically applied antiseptics act superficially on the surface of a lesion and do not necessarily penetrate deeply into the tissues at the site of action of an inflammatory process. Thus, only the microorganisms on the mucosal surface are killed, while those deep in an inflammatory process are untouched. Third, antiseptics may also kill indigenous oral microorganisms which maintain a delicate balance between the nonpathogenic and pathogenic microbial population of the mouth. Fourth, the action of antimicrobial agent has been diluted or eliminate by salivation and swallowing, the growth of the organism resumes. Fifth, antimicrobial agents may lead to development of resistant strains of pathogens that persist in the mouth and throat and kill or injure some of the cells of the host. Sixth, they may lower the "resistance" of host tissues by nullifying the actions of immune substances in the mucosa (IgA, IgG, and IgM antibodies). Seventh, no conclusive data are available from controlled studies to show that no harm results from long-term use of antimicrobial agents on a day-to-day basis for prophylactic purposes in the absence of a pathologic process. Eighth, data on delayed toxic effects from long-term use are not available. Ninth, conclusive controlled studies are not available to show that a health benefit results from long-term use of antimicrobial agents applied to the oral cavity on a day-to-day basis for prophylactic or therapeutic purposes.

The Panel has referred to the conclusions of a previous Commissioner of the FDA on the lack of evidence of effectiveness of gargles and mouthwashes containing antimicrobial ingredients from data submitted by the NAS/NRC. (See part II. paragraph B.5. above—Dosage forms of oral health care products.)

The Panel is also mindful of the position of the Council on Dental Therapeutics (Ref. 1):

> Many germicidal claims are included in mouthwash advertising directed either to the dentists or to the public. Attention should therefore be directed to the following considerations: (1) No method is yet available to give a thoroughly satisfactory comparison of germicidal agents in a test tube with the same agents under the actual conditions of their use in the oral cavity. (2) There is no adequate evidence that the average person benefits by a nonspecific change in the oral flora. (3) Some uncertainty still exists concerning the role of microorganisms as etiologic agents of many oral diseases.

OTC oral health care products are the only products containing antimicrobial agents that are used for protracted periods of time on a day-to-day basis, perhaps even spanning a lifetime. They are used for medicinal purposes when no symptoms exist or when no obvious signs of a disease are present and without any direct advice or sanction by a physician or a dentist. The Panel, therefore, concludes that antimicrobial agents should be used for oral health care only when specific symptoms, (e.g., sore throat or sore mouth) are present justifying the need for a specific product whose effectiveness has been established.

**Reference**

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 38th Ed., American Dental Association, Chicago, p. 343, 1979.

3. *Mode of action.* The following discussion is based on a review of several sources (Refs. 1 through 6).

Antiseptics and disinfectants exert their antimicrobial activity in a variety of ways. They may act by coagulation or denaturation of protoplasmic proteins. The phenols and certain metallic agents, such as derivatives of mercury, zinc, and aluminum, and alcohols act in this manner. Some cause cell lysis (alteration of cell membranes that causes leakage of protoplasm). They may be "surface-acting" substances which decrease the permeability of a cell by lowering surface tension at the cell membrane and fluid interface. The quaternary nitrogenous compounds or the "quats" act in this manner. (Since "the quats" are widely used in OTC oral health care products, their mechanisms of action are described in more detail below. (See part IV. paragraph A.8. below—Quaternary nitrogenous cationic antimicrobial agents.) Others act by the denaturation and inactivation of enzymes, which interferes with the metabolic activity of the cell. Some apparently penetrate into the interior of the cell by virtue of their lipid solubility and alter the intracellular biochemical activities in the membrane and within the cell. Some are oxidizing agents that act on the cell membrane or penetrate into the cells and alter the chemical structures of cellular constituents or metabolic activities of the cell.

Penetration of antimicrobial agents into the cell usually occurs by simple diffusion. It can be facilitated by substances in the extracellular fluid that decrease their solubility in the surrounding medium. Some antimicrobial agents may accumulate on the cell surface by adsorption and surround the microorganism with a dense layer of the agent resulting in altered cell permeability which makes the cell unable to function. Mercuric chloride may act in this manner. Certain antiseptics, such as phenol, that enter the cell by simple diffusion do not necessarily accumulate in its interior. They continue to penetrate into the cell and alter its structure and physiological activity. The concentration in the cell is no greater than the concentration in the solution surrounding it, but it continues to act as it moves inward. This attribute limits the safety of phenolic compounds because they act in the same manner on tissue cells of the host.

Most chemical agents that are used for topical antisepsis do not act selectively and do not exert their adverse effects solely on the microorganism. They generally injure both the cells of the host and the microorganism. The harm that results to healthy tissue cells occasionally offsets any beneficial effects that might be obtained by the action of an antiseptic.

The effectiveness of antiseptics depends upon the concentration in the medium in which it is dissolved, duration of contact with the microorganism, pH of the surrounding medium, the environmental temperature, and the presence of inorganic or organic matter. The latter may nullify the activity of many of the effective antimicrobial ingredients.

Different species of microorganisms vary in their resistance and susceptibility to an antimicrobial agent. Different cultures of the same microorganism and even different individual microorganisms in the same culture may exhibit marked variations in susceptibility to a particular antimicrobial agent.

The efficiency of any disinfectant depends on the concentration that comes into contact with the microorganism and its duration of contact. Thus, a solution of mercuric chloride whose concentration is 1:3,000 is more efficient that one whose concentration is 1:10,000. Exposure to the more concentrated solution for 2 minutes kills more microorganisms than exposure to the more dilute solution for 5 minutes. However, germicidal activity is not necessarily directly proportional to concentration. For example, concentrations of alcohol above 95 percent kill bacteria less rapidly than the 70 percent to 95 percent concentration range. Another factor that influences efficiency is the temperature

of an antiseptic to which the microorganisms are exposed. It is known that when a portion of a culture of microorganisms is added to an antiseptic solution which is maintained at a room temperature of about 20 to 25° C, far fewer organisms are killed than if the mixture were kept at 30° C, or more importantly, at a physiological body temperature of 37° C.

The effect that a solution of an antiseptic exerts usually varies inversely with the number of microorganisms present, because each microorganism withdraws a certain amount of the antiseptic from the solution and thus reduces its overall concentration. The presence of proteins has the same influence as the microorganisms in reducing the overall concentration of the antimicrobial agent in the solution. The proteins offer the antiseptics the same surface area for adsorption or combine with some of the antimicrobial agents in the same manner as do the proteins of the microorganisms. Thus, a concentration of an antimicrobial agent which is sufficient to sterilize water infected with bacteria may have little or no effect if applied to a suppurating (pus-producing) wound. The greater part of the antimicrobial agent combines with the protein in the wound; the amount that remains in the solution may be too dilute to act on the microorganisms. Therefore, many substances which are effective antimicrobial agents in aqueous or other types of solutions lose their antimicrobial activity in protein solutions. This phenomenon was one commonly referred to as the "protective action of colloids," and is due to the formation of combinations of the antiseptic with the proteins, which usually results in precipitates. These products are not dangerous to the host but they are comparatively innocuous and exert no effect on the microorganisms in the tissues. The inhibiting action of proteins may also be due partly to the fact that they limit the diffusion of an antimicrobial agent into a cell. In fact, many antimicrobial agent act on proteins generally, and are not specifically toxic fo a given type of microorganism. The lipids, like the proteins, may also lower the potency of an antimicrobial agents by combining with the agent and reducing its effective concentration.

If an antimicrobial agent is to penetrate into the interior of an organism in an effective quantity, it must be as soluble in the protoplasm as it is in the fluid in which it is incorporated. The antimicrobial agent will not leave a medium in which it is readily soluble for one in which it is less soluble. Members of the aromatic series of antimicrobial agents are very soluble in fats and oils; however, fats and oils are not suitable media for application to the infected tissues because the drug remains in the oily menstruum and fails to penetrate into the microorganism.

Mercuric chloride dissolved in alcohol has little germicidal activity. This is due to the fact that mercuric chloride, as well as salts of other heavy metals, is not dissociated (ionized) in alcohol (95 percent). The antimicrobial activity is due to the ions of metal and not to the un-ionized molecules. In order for a salt to be active it must be dissociated (ionized), and this process requires the presence of water. If the mercuric chloride is dissolved in dilute alcohol (25 percent) its effectiveness is increased because much of it is ionized, facilitating penetration of the components of the salt into the cell. The addition of inorganic salts to an aqueous solution of phenol often increases its antimicrobial activity because the solubility of the drug in water is decreased and there is a greater tendency for it to pass from the water into the interior of the microorganism.

There is some evidence to indicate that solutions containing several antimicrobial agents are more strongly antiseptic than those containing single-entity ingredients. For example, a mixture of phenol and mercuric chloride, each at less than its minimum effective concentration, is more effective as an antimicrobial agent than more concentrated solutions of either alone. This is not a hard-and-fast rule, however, and a combination may have the opposite effect. Therefore, combinations, and the concentrations of ingredients in them, must be considered individually. It is the consensus of the Panel that these drugs are all protoplasmic poisons and may harm both the cells of the host as well as the pathogenic organism. For the sake of safety, preparations containing single-entity active ingredients are preferred.

Some OTC products contain less than the minimum inhibitory concentration of a chemical. Such solutions merely retard the growth of microorganisms. Concentrations of substances that are too dilute to kill microorganisms are bacteriostatic and may merely act as preservatives. Antiseptic claims cannot be made for them and to do so is both misleading and a misbranding of a product.

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4. *The microbiology of the oral cavity*—a. *Changes of the oral flora with age.* The oral flora changes from birth through the primary, mixed, and permanent dentitions. There are also differences in the oral flora following extraction of all the teeth and their replacement with dentures. The oral cavity normally supports a concentrated and varied microbial population, the heaviest concentrations being on the dorsum of the tongue, around the gingival sulcus, and on the surfaces of the teeth.

At birth, the oral cavity is usually sterile despite inoculation with the indigenous flora of the mother's genital tract, which is comprised of lactobacilli, corynebacteria, micrococci, coliforms, aerobic and anaerobic streptococci, yeasts, protozoa, and sometimes viruses. The first 8 hours following birth show a rapid increase in the number of detectable organisms. For the first few days of life, the bacterial composition varies considerably. The organisms have been reported to include several species of lactobacilli, streptococci, staphylococci, pneumococci, enterococci, veillonellae, anaerobic streptococci, coliforms, sarcina, and neisseriae. With the exception of *Streptococcus salivarius,* most of these organisms are found sporadically but not in high numbers. The newborn's mouth is highly selective even within the first few days. Practically none of the bacteria common to the general environment become established, and only a few of the microorganisms inhabiting adult mouths occur persistently at this time.

By the end of the third month, all mouths support a microbiota beginning to resemble that of the adult. At the end of the first year of life, however, only streptococci, staphylococci, veillonellae, and neisseriae are generally found in all

mouths. Actinomyces, nocardiae, lactobacilli, and fusobacteria can be cultured from about one-half of the mouths. Bacteroides, leptotrichiae, corynebacteria, and coliforms are isolated from less than half of the mouths. Streptococci still predominate numerically. Infancy is dominated by facultative species, to which are gradually added the various obligate anaerobes, but numerically the facultative types generally dominate at all ages (Refs. 1 and 2).

In preschool children, the proportions of predominant cultivable organisms from the gingival crevice area resemble those in adults, except that *Bacteroides melaninogenicus* and spirochetes are not present in all children. *Bacteroides melaninogenicus* is present in virtually all adolescents. Spirochetes also increase in incidence with age. The presence of dental caries (cavities) also influences the oral flora by providing new ecological niches for multiplication, new substrates, and a more acidic pH.

Tables 1 and 2 shows the predominant genera and species found in various sites (Ref. 2).

With the loss of teeth, spirochetes, lactobacilli, and some strains of streptococci are reduced. Shklair and Mazzarella's (Ref. 3) studies demonstrated that lactobacilli and yeasts virtually disappear during the edentulous period and that *Streptococcus salivarius* increases. During the first 2 weeks after placement of the dentures, streptococci remain at a high level while lactobacilli and yeasts gradually return, but remain at a low level. After 3 to 5 weeks the lactobacilli and yeasts increase, and the streptococci decrease to preextraction levels. During the entire period, the number of staphylococci do not fluctuate significantly.

TABLE 1.—MEAN PERCENTAGES OF CULTIVABLE ORGANISMS IN THE ADULT ORAL CAVITY (Ref. 2)

| Organism | Saliva | Percentage | | Tongue |
|---|---|---|---|---|
| | | Gingival crevice area | Dental plaque | |
| Gram-Positive Facultative: | | | | |
| Cocci | 46.2 | 28.2 | 28.2 | 44.8 |
| Streptococci | 41.0 | 27.1 | 27.9 | 38.3 |
| *Streptococcus salivarius* | 4.6 | N.D. | N.D. | 8.2 |
| Enterococci | 1.3 | N.D. | N.D. | 7.2 |
| Staphylococci | 4.0 | 1.7 | 0.3 | 6.5 |
| Gram-Positive Anaerobic: | | | | |
| Cocci | 13.0 | 7.4 | 12.6 | 4.2 |
| Gram-Negative Facultative: | | | | |
| Cocci | 1.2 | 0.4 | 0.4 | 3.4 |
| Gram-Negative Anaerobic: | | | | |
| Cocci | 15.9 | 10.7 | 6.4 | 16.0 |
| Gram-Positive Facultative: | | | | |
| Rods | 11.8 | 15.3 | 23.8 | 13.0 |
| Gram-Positive Anaerobic: | | | | |
| Rods | 4.8 | 20.2 | 18.4 | 8.2 |
| Gram-Negative Facultative: | | | | |
| Rods | 2.3 | 1.2 | N.D. | 3.2 |
| Gram-Negative Anaerobic: | | | | |
| Rods | 4.8 | 16.1 | 10.4 | 8.2 |
| Fusobacterium | 0.3 | 1.9 | 4.1 | 0.7 |
| *Bacteroides melaninogenicus* | N.D. | 4.7 | N.D. | 0.2 |
| *Vibrio sputorum* | 2.1 | 3.8 | 1.3 | 2.2 |
| Other Bacteroides | 2.4 | 5.6 | 4.8 | 5.1 |
| Spirochetes | N.D. | 1.0 | N.D. | N.D. |

N.D. = not detected.

TABLE 2.—PERCENT DISTRIBUTION OF ORGANISMS IN DIFFERENT SITES IN THE HUMAN ORAL CAVITY (REF. 2)

| Organism | Supragingival plaque | Tongue | Gingival crevice | Cheek | Saliva |
|---|---|---|---|---|---|
| *S. mutans* | 3.9 | 0.3 | | 0.5 | 0.2 |
| *S. sanguis** | 75.0 | 9.0 | | 29.0 | 47.0 |
| *S. salivarius** | 0.7 | 55.3 | 0.5 | 10.7 | 47.4 |
| *B. melaninogenicus*** | 0.3 | 0.4 | 4.5 | 0.3 | 0.42 |
| Spirochetes*** | 0.1 | | 1.5 | | |
| Lactobacillus | 0.0001 | | | | 0.01 |

*Percent of facultative streptococci.
**Percent of total cultivable flora.
***Percent of microscopic count.

b. *Problems associated with the study of the oral microbial flora.* It is difficult to obtain definitive information concerning the location, kinds, and numbers of oral microorganisms because of problems of variability, sampling, cultivation, enumeration, and identification. Even in a single mouth the microbial population undergoes progressive changes until maturity, and there are wide fluctuations thereafter.

Diet plays an important role in the growth of microoganisms as do the host tissues and other microoganisms. The nature and amount of proteins and carbohydrates will determine which organisms will flourish and which will remain static. The amount of sucrose in the diet can influence the amount of plaque, the population density, and the percentage of *Streptococcus mutans* and *Streptococcus sanguis* in the plaque.

Essential metabolites for some bacteria are produced by other bacteria. For example, formic and lactic acids produced by bacteria in the oral cavity in part supply the energy sources for *Veillonella alcalescens.*

The bacteria from the human oral cavity have a wide variety of oxygen tension requirements. Obligate aerobes facultative aerobes, microaerophiles, anaerobes which tolerate oxygen exposure but multiply only in its absence, and strict anearobes which will not survive even momentary exposure to oxygen, have all been identified.

c. *The organisms comprising the oral microbiota.* The number of so-called species of bacteria indigenous to the oral cavity are innumerable since their

recovery depends greatly upon the methodology used for their cultivation. The variations from person to person and from site to site are great. The recent use of anaerobic transport solutions for the specimen and the anaerobic chamber for all manipulations during cultivation have increased enormously the number of genera and species which are associated with various areas of the mouth, especially that of the gingival crevice and periodontal pocket.

Mycoplasma species can be demonstrated in all adult mouths. They have been isolated from saliva, plaque, and calculus; they have also been isolated from samples obtained from healthy and diseased gingival crevices and various lesions. Protozoa can be demonstrated in small numbers in approximately 50 percent of clean and healthy mouths. A much higher incidence is associated with poor oral health care and periodontitis (Ref. 1).

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5. *The mircobial flora of the pharynx and upper respiratory tract.* The bacterial flora of the oral cavity and that of the pharynx and upper airways are, in most respects, not remarkably different, since there is an intermingling of the secretions of the mouth and throat. However, there is a gradual transition in composition along the pathway from the lips, gums, mouth, and throat into the trachea and bronchi. As is the case in the oral cavity, the ecology, i.e., the relationships between organisms and interrelationships between the organisms and their environment, is important (Refs. 1 through 6). In the mouth, numerous microbial species reside in the oral and hypopharynx and the upper respiratory tract of man under normal conditions. Some are regularly demonstrable as major permanent residents. These include many species of streptococci, both faculative and anaerobic, with the alpha hemolythic "viridans group" predominant, leptothrichia, several species of corynebacteria ("diphtheroids"), a variety of neisseria species (e.g. *Neisseria catarrhalis, Neisseria pharyngitidis*). as well as the potentially pathogenic *Staphylococcus aureus.* Anaerobes includes the veillonella, vibrios, spirochetes, fusobacteria, bacteroides, and many others too numerous to list here. In addition, coliform bacteria, proteus, pseudomonas, and others which are predominant residents of the normal intestinal flora may occasionally reside in the mouth and throat in small numbers. Pathogenic microorganisms may exist within the indigenous oral flora of persons who have recovered from some infectious disease process. These have established an equilibrium with the other organisms ordinarily present and exist without causing a pathologic process. Persons harboring such microorganisms may, of course, be carriers and may be a source of infection for other persons with whom they have contact (Ref. 4).

Knowledge of the composition of the indigenous microbial flora of the naso-, oro-, and laryngopharynx is just as important as knowledge of the composition of the indigenous microbial flora of the oral cavity. For instance, in evaluating laboratory reports concerning bacteriological examination of clinical specimens, the physician must often judge whether the isolated organisms are indigenous flora and can be disregarded, or are pathogenic and may cause symptoms in an individual patient. Marked differences in the composition of the indigenous microbial flora may be observed among different individuals. These differences depend upon numerous variable factors, such as pH and viscosity and composition of the saliva. Various degrees of compatibility exist among groups of bacteria, based on differences in metabolic activities and growth requirements. In addition, variable factors in the host may be equally as important, if not more important, in creating a specific ecological composition and equilibrium of the bacterial flora. Living habits, food preferences, hormonal or metabolic peculiarities, and other factors probably exert specific influences in determining the nature of the microbial flora of the naso-, oro-, and hypropharynx (Ref. 4).

The existence of an ecological balance between various types of microorganisms supports the concept that the indigenous flora serves as a strong and an effective natural barrier against invading pathogens. In many instances, the invader encounters an environment which is unfavorable to its gaining a foothold and surviving within the biosystem of the existing flora. Any disturbance of the indigenous flora, however, can create an environemnt which could give invading pathogens an opportunity to gain a foothold and establish residence in the upper air passages. Even an imbalance among microorganisms ordinarily present in the indigenous flora can lead to multiplication of their numbers and a pathological state, since some microorganisms that are normally present may be opportunistic pathogens. It is for this reason that the use of antimicrobial agents in the absence of symptoms of a pathologic state is considered irrational and possible harmful (Ref. 4).

Disturbances of the normal flora of the throat may occur from many causes. Some are due to local factors, some to general factors, and some to a combination of both general and local factors. Chemical or physical irritation, local allergic reactions, and anatomical abnormalities, such as mucosal atrophy or functional changes, may have a direct local effect on the bacterial flora. Causative factors of a systemic nature include nutritional deficiencies, avitaminosis, unbalanced metabolic disorders (diabetes), and other similar pathological states. However, the most frequent and also in most cases a dangerous cause is the unwarranied use of antimicrobial agents. All types of antimicrobial agents can be incriminated but most noteworthy are the antibiotics. For whatever reason and in whatever form antibiotics are administered to a patient, they may alter the normal bacterial flora because the drug-susceptible microorganisms will be killed or their metabolic activity inhibited. Often no overt consequence follows the use of an antibiotic and the flora shifts back to its previous composition and equilibrium when use of the drug is discontinued. In some cases, and organism develops mechanisms that overcome adverse effects of the antibiotic and continues to proliferate in its presence. This phenomenon, called drug resistance, occurs frequently. The danger of a disease process resulting from an alteration of the compositon of the indigenous bacterial flora must not be underestimated; moreover, the possibility of the occurrence of this response is of equal importance as the development of drug resistance (Ref. 4).

a. *Disease-producing properties of microorganisms.* Some organisms, especially fungi, cause disease simply by their presence in the tissue. The tissue responds by developing a foreign body reaction with the subsequent formation of granulomas. As the microorganisms multiply and consume nutrients, inadequate nourishment of the tissue may lead to irreversible damage

or even necrosis. Fungal infections are more apt to cause sore mouth than sore throat.

Many gram-negative microorganisms contain endotoxins. These are complex molecules consisting of a protein combined with a liposaccharide. When released in the tissues of a host they cause toxic manifestations. The endotoxins are usually present in the cell wall of the microorganism. They are released upon death and disintegration of the microbial cells and pass into the tissue fluids or blood. Free endotoxin causes local edema, hemorrhage, and possibly necrosis. Bloodborne endotoxins cause systemic generalized symptoms that include, fever, nausea, vomiting, diarrhea, oliguria, hematuria, and even anuria. Shock of various degrees, dependent on the amount and virulence of the endotoxin liberated into the circulation, is a common manifestation.

Other microorganisms produce exotoxins which are excreted locally into their environment where they are absorbed, become bloodborne, and act systemically. Most exotoxin producers are of the gram-positive type, including *Staphylococcus aureus,* which is often indigenous in the mouth, and *Strepotococcus pyogenes.* Minute amounts of an exotoxzin are sufficient to cause severe damage to specific organ or cell systems. These organs or cell systems may be distant from the focus of infection.

Some microorganisms release enzymes, which increase their invasiveness. A great variety of important pathogenic enzymes elaborated by microorganims have been described. The organisms involved in their production include *Strepotococcus pyogenes* and *Stapohylococcus aureus.* The enzymes elaborated include hyaluronidase, proteinases, fibrinolysins, collagenases, and numerous others, most of which may facilitate spread of infection in the tissue (Ref. 4).

(1) *Streptococci.* Streptococci are found in the throats of both human beings and animals. *Streptococcus pyogenes* may cause severe sore throat and generalized systemic manifestations, such as fever, joint pains, etc. They are grounded on the basis of antigenic properties, and these groups possess varying degrees of host specificity. Group A streptococci (*Streptococcus pyogenes*) cause 90 percent of the streptococcal infections in human beings. The natural reservoir of human pathogenic streptococci is the respiratory tract of persons who have developed an immunologic equilibrium with these bacteria and are asymptomatic carriers. Other groups of pathogenic streptococci are found under similar conditions in various animal species. Nonpathogenic streptococci are abundant among the indigenous flora of the upper respiratory tract and mouth. They inlcude the "viridans groups" of streptococci found in the mouth and throat, enterococci (including group D-streptococci) found in the mouth and oropharynx, as well as anaerobic streptococci (e.g. peptostreptococcus) found in the respiratory tract and mouth. Any of these strains can, under certain conditions, become pathogenic. Such pathogenicity may be expressed when the equilibrium of the indigenous oral flora is disturbed or when the organisms are introduced into other areas of the body which they do not normally inhabit. Typical examples of disease processes they may cause are dental pulpitis, periodontal abscesses and subacute bacterial endocarditis (usually due to the "viridans group" of streptococci).

About half the human population develops a delayed type of hypersensitivity against streptococcal substances. This can be demonstrated by skin testing with streptococcal extract (Refs. 1 through 4).

(2) *Pneumococci.* Pneumococci are closely related to streptococci and, if pathogenic, most often cause bacterial penumonia. Certain antigenic types are particularly apt to produce disease; others are seldom pathogenic and are part of the indigenous flora of the upper respiratory tract. They may become pathogenic if the bacterial flora is altered and an imbalance occurs. Such an alteration may occur from the unwarranted use of antimicorbial agents.

(3) *Staphylococci.* The important pathogenic member in this group is *Staphylococcus aureus* which causes purulent infections in animals and human beings alike. It is ubiquitously present on the skin and in the nose and throat. Usually a well-balanced equilibrium exists between the host and this type of microorganism. This equilibrum may be disturbed by mechanical irritation, allergic reactions of the mucous membranes, traumatic lesions, nutritional deficiencies or hormonal imbalances, such as occurs in diabetes, thyroid disease, and so forth. Patients may acquire antimicrobial-resistant staphylococci and incorporate them into their normal bacterial flora, especially in hospital environments. If a resident strain of *Staphylococcus aureus* is antimicrobial-resistant, application of the particular antimicrobial agent would give the organism a growth advantage by killing or inhibiting the growth of organisms that are antagonistic to the staphylococcus (Ref. 4).

(4) *Neisseria.* Several species of non-pathogenic neisseria are part of the indigenous flora in the pharynx and upper respiratory tract. Among these are *Neisseria catarrhalis* and *Neisseria pharyngitidis.* The pathogenic members of this genus, *Neisseria meningitidis* and *Neisseria gonorrhoeae,* cause disease exclusively in human beings. *Neisseria meningitidis* inhabits the throat of about 5 percent of normal persons but shows little tendency to spread to noncarriers. Restricted outbreaks of meningococcal meningitis occur in special epidemiological situations, usually among people who live in crowded conditions. The species of *Neisseria meningitidis* can be subdivided into three serological types: A, B, and C. Type B is now encountered most often in epidemics, whereas 1 or 2 decades ago type A was more prominent. Type C is occasionally found in sporadic infections (Ref. 4).

(5) *Corynebacteria.* Nonpathogenic corynebacteria (diphtheroids) constitute a large portion of the indigenous flora of the mucous membranes of the throat.

(6) *Haemophilus influenzae. Haemophilus influenzae* is frequently found in the respiratory tract of normal persons. If the organism lacks a capsule, it is usually avirulent. Primary infections due to capsulated strains occur, especially in children. Severe forms of the disease may also cause meningitis. *Haemophilus influenzae,* as in the case with streptococci, pneumococci, or staphylococci, may play a role in secondary bacterial infections of viral diseases such as influenza-pneumonia. In fact, it was considered by its discoverer to be the etiological agent of influenza.

(7) *Mycobacteria.* The two diseases caused by mycobacteria are tuberculosis and leprosy. Both may cause infections in the throat and larynx, although these are rare. The manifestations are usually part of a chronic pulmonary or other systemic infection (Ref. 4).

(8) *Spirochetes.* Three genera of human pathogenic spirochetes are recognized: borrelia, treponema, and leptospira. Only the first two are of special interest in oral diseases. Both genera contain species which are components of the indigenous flora. They may become opportunistic pathogens, as is the case with *Borrelia vincenti,* which is associated with Vincent's angina, cancrum oris, and gangrenous processes in the throat and other parts of the upper respiratory tract. *Treponema pallidum,* the

causative agent of syphilis, is of interest since in the secondary phase of the disease it is particularly apt to cause pharyngitis.

The Panel emphasizes that infections caused by the aforementioned bacteria are not "minor," may be serious and require the expertise of a dentist or physician, as well as a microbiologist for their recognition. The conditions they cause are not amenable to self-diagnosis and unsupervised self-treatment with antimicrobial and other health care products.

b. *Viruses causing disease of the oropharynx.* The number of respiratory tract diseases caused by viruses is indeed great. Over 250 viruses are believed to cause the common cold. Current treatment of viral infections involves active and passive immunoprophylaxis. None of the agents used for this purpose are available OTC. OTC antimicrobial agents are of no therapeutic benefit (Ref. 5).

Viruses causing disease of the throat include the coxsackie A virus, herpes virus, infectious mononucleosis virus, and mumps virus. Other viruses which primarily cause acute pharyngitis are discussed below.

(1) *Coxsackie A virus.* Several serological types of coxsackie A viruses have been associated with lesions of the mouth and oropharynx. There are at least 23 immunologically distinct coxsackie A types. The coxsackie A viruses have been shown to cause not only respiratory tract disease but also aseptic meningitis, paralysis, exanthemas, and hepatitis (Ref. 5).

Herpangina is a clinical syndrome which occurs mostly in the summer and mainly affects children. The illness is featured by an acute onset of fever, sore throat, and dysphagia. It is sometimes accompanied by abdominal pain, myalgia, headache, and vomiting. The characteristic feature of the syndrome is the presence of small, scattered vesicles in the oropharynx, each surrounded by an erythematous zone. They are located on the anterior pillars of the fauces, but can also occur on the palate, uvula, tonsils, and tongue. They do not usually occur on the gingival or buccal mucosa. The individual lesion appears first as a grayish white papule or vesicle about 1 to 2 mm in diameter which is surrounded by a red areola. After several days the areola becomes more intensely red, the vesicles enlarge and become shallow grayish ulcers. Both vesicles and ulcers may be present at the same time. Usually there are 4 to 5 lesions, but as many as 14 or 15 have been seen. The course of the illness is usually benign. There have been reports of parotitis complicating herpangina.

Coxsackie A–10 has been associated with an epidemic of acute lymphonodular pharyngitis in children. The patients had fever, headache, and sore throat from 4 to 14 days. The distinct lesions were discrete whitish or yellowish nodular papules on the uvula, anterior pillars, and posterior pharynx which did not vesicate. Histological examination of the nodules revealed the papules to be formed of tightly packed lymphocytes. There is no specific treatment for coxsackie A disease (Ref. 5).

(2) *Infectious mononucleosis.* Infectious mononucleosis (IM) is an acute infectious disease of presumed viral etiology, which causes sore throat, that occurs predominantly in children and young adults. The search for the etiology of IM is closely associated with the Epstein-Barr (EB) virus. The EB virus is a member of the herpes group and was first detected in cultures of Burkitt's lymphoma cells. The association of the virus with IM is based on a serological relationship. Individuals with IM develop antibody to EB virus in their serum (Ref. 5).

(3) *Viral upper respiratory diseases.* Although exact data are difficult to obtain, it is generally agreed by most authorities that acute upper respiratory tract infections (URI or the common cold) are the greatest cause of morbidity in the United States (Ref. 5).

Viral respiratory illnesses are caused by numerous groups of viruses. The viruses produce a variety of clinical syndromes. Any individual virus group is capable of causing a multiplicity of syndromes, and a particular syndrome can be caused by various groups of viruses.

There appears to be a difference in the morbidity caused by these viruses in children and in adults. This is probably the result of the acquired immunity, which is present in adults and not in children.

The verification that the disease is of viral etiology is wholly dependent upon laboratory tests (Ref. 5).

(4) *Adenoviruses.* The adenoviruses were first isolated in 1953 by culturing adenoid tissue from children undergoing adenoidectomy. At least 31 immunologically distinct adenoviruses have been identified, 9 of which have been associated with respiratory tract infections. Synonyms are adenoid degeneration (AD) agents, acute respiratory disease (ARD) viruses, and adenoidal-pharyngeal-conjunctival (APC) viruses.

The clinical syndromes associated with adenovirus infections include undifferentiated acute respiratory disease, pharyngoconjunctival fever, and pneumonia. Clincial signs of undifferentiated acute respiratory disease include sore throat (pharyngitis), cervical lymphadenopathy, cough, chills, fever, malaise, and headache. Coryza and fever may be present. The clinical signs of pharyngoconjunctival fever include fever, pharyngitis, conjunctivitis, and frequently gastrointestinal pain. Pneumonia or severe respiratory tract involvement occasionally occurs (Ref. 5).

(5) *Influenza viruses.* Influenza viruses, which are members of the myxovirus family have had a profound effect on people. Pandemics of influenza have taken severe tolls in morbidity and mortality throughout history. These pandemics have been due to alteration in the antigenic makeup of influenza viruses approximately every 10 years for the past 30 years.

The influenza viruses are divided into three types, A, B, and C, on the basis of their neucleocapsid and M protein antigens. Each type is further divided into antigenic subtypes, which differ from each other by the composition of their surface glycoproteins (hemagglutinin and neuraminidase). A continuous genetic shifting of the antigenic configuration of the viruses creates "new" viruses for which the population has no antibodies and, therefore, immunity most likely has resulted in pandemics of influenza (Ref. 1, 2, 3, 5, and 7).

Influenza viruses can cause a wide spectrum of respiratory tract disease, ranging from subclinical infection to fulminating pneumonia. However, the typical case of influenza is a systemic disease which is familiar to all physicians. After a short incubation period of one to three days, coryza, cough, sore throat, headache, fever, malaise, anorexia, and frequently nausea and vomiting occur accompanied by an apathetic appearance. The illness persists for a week to 120 days and is usually followed by a prolonged period of convalescence in which the patient is somewhat lethargic or "not up to par." Pneumonia, either of purely viral origin or caused by a secondary bacterial invader, or of a mixed infection of viral and bacterial etiology, is the most common complication. Other complications are meningoencephalitis and myocarditis, but these are quite rare (Ref. 5).

(6) *Para-influenza viruses.* The para-influenza viruses were first isolated during the 1950's. Four distinct serologic types have been recovered in the throat of human beings (Ref. 5).

(7) *Rhinoviruses.* The rhinoviruses are the most recently isolated viruses to be

referred to as "the common cold virus." The initial rhinovirus isolates were made in 1954 from afebrile individuals with coryza, sore throat, and cough. There are probably over 100 distinct serological strains of rhinoviruses. Currently some 60 specific serological types have been classified. No antimicrobial agents are available that exert any therapeutic effect on these viruses. The common cold is actually a misnomer since so many different viruses can afflict people and cause similar symptoms, coryza, sore throat, and systemic manifestations such as malaise, fever, etc. The term might be considered a proper one to use if the symptom complex were caused by a single virus (Ref. 5).

(8) *Coronaviruses.* The coronaviruses are a relatively newly described group of viruses which are also associated with the common cold. The name is derived from the fact that, when visualized with the electron micrograph, the human coronavirus resembles a crown (Ref. 5).

c. *Fungal infections.* Fungal infections, also known as mycoses, have been playing an increasingly important role in conditions affecting the mouth, nose, and throat for several reasons: (1) There is greater awareness of their presence; (2) better diagnostic facilities are available; (3) the incidence is increased because of therapeutic interference (antibiotics, immunosuppressive drugs, radiation); and (4) there is increased longevity in such diseases as lymphomas, other neoplasms, and hematologic disorders (Ref. 6).

Conditions favorable to the development of mycoses prevail in the mouth and throat, where a moist, warm environment, and such crevices as tonsillar crypts and periodontal spaces encourage growth. They are also found in the nasopharynx and nose where such conditions as obstructive lesions and deviated nasal septa favor the growth of fungi and related organisms. Actinomyces and nocardia are now universally accepted as bacteria, but are traditionally discussed with fungi because of the close resemblance between the symptomatology and course of the diseases they cause. A discussion of the oral and pharyngeal lesions most commonly due to fungal infections can be found earlier in this document. (See part II. paragraph B.4.b. above—Sore mouth.)

The diagnosis of mycosis depends upon the availability of a well-equipped laboratory and the use of modern immunologic and staining procedures. Contrary to widespread belief, biopsies and not cultures are the most rapid and commonly successful tools for diagnosis of fungal disease. Biopsy material should be divided into two specimens, one for cultural studies and one for staining. The selection of proper media by the laboratory is necessary since some organisms require special cultural conditions (Ref. 6).

Candidiasis, the fungal disease which occurs in the mouth most commonly, is caused by the yeast-like organism *Candida albicans.* It covers a wide range of manifestations. (See part II. paragraph B.4.b. above—Sore Mouth.) Candidiasis is most often found about the oropharynx. The small yeast (2 to 5 um) is ovoid, appears intensely blue with the Gram stain, and can be demonstrated with any of the numerous stains for fungi. Broad hyphae can be seen in association with the yeast cells. Often it is quite obvious that the hyphae are just elongated yeast cells when budding takes place at the point of constriction. The incidence of *Candida albicans* in the mouth and throat varies from country to country and depends on age, hygiene, presence of other diseases, use of broad-spectrum antibiotic therapy, and so forth (Ref. 6).

A mild form of candidiasis is thrush, a white to grayish membranous formation over tonsils or adjacent mucosae, which occurs either in discrete or confluent specks and which can often be removed with a swab. Smears of such membranes rule out diseases such as diphtheria, the ulcerations of infectious mononucleosis, or acute leukemia. Thrush is seen most often at the extremes of age, in the (often premature) newborn who acquire the disease in the maternal birth canal, and in the geriatric patient, dying of old age or from tumors. Thrush, therefore, is often a warning signal of some profound abnormality existing in the body and does not itself require energetic therapeutic measures (Ref. 6).

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6. *Evaluation of antimicrobial activity.* One of the requests made of the Panel was to recommend testing procedures whereby a Category III product could be reclassified to Category I. The Panel has made such recommendations and suggestions concerning testing for antimicrobial ingredients for oral health care products. (See part IV. paragraph C. below—Data Required for Evaluation.) The Panel has suggested a general in vitro test that may be used as a guide, but which may be modified to suit individual protocols for testing a specific ingredient for specific purposes.

It is the concensus of the Panel that it is not possible to suggest an in vivo method of a general type that would encompass all criteria necessary to evaluate the effectiveness of all antimicrobial agents claimed to be effective in relieving symptoms of sore throat and sore mouth due to antimicrobial activity. The Panel had considered an in vivo method based on plaque reduction on the teeth and periodontal tissues as a criterion for antimicrobial activity in the oral cavity, but discarded it because it became obvious that it was inexact and had no rational basis since dental plaque is not a disease per se (Ref. 1 through 4). Moreover, the Panel was not charged with reviewing products used to treat dental or periodontal diseases. Some clinicians and microbiologists specializing in dental microbiology have used plaque reduction as a criterion of effectiveness of antimicrobial agents in mouthwashes and have submitted data in support of their effectiveness of such products based on this concept. The rationality of plaque reduction as a criterion of effectiveness of antimicrobial agents for use in the mouth and throat is highly debatable, and evidence of the validity of the method is scant. Plaque reduction, therefore, is not accepted by this Panel as a criterion for determining effectiveness of antimicrobial agents for oral health care products intended to treat sore mouth or sore throat.

Dental plaque has been described as a soft and tenacious material found on surfaces of teeth readily removed by mechanical means such as brushing or flossing, but not readily removed by rinsing with water and other solutions (Ref. 5). The composition of plaque is multivaried, consisting of proteins, carbohydrates, clumps of microorganisms, and other organic and inorganic materials. The amount, as well as the microbial and biochemical composition of plaque, varies with the site of formation, the duration of accumulation, the composition of the diet, and perhaps other undetermined factors (Ref. 6). Both dental caries and periodontal disease are attributed to plaque. The Panel, however, was not charged to consider dental plaque and periodontal diseases. The Panel has never stated that plaque is not involved in causing dental caries and periodontal diseases.

It is noteworthy that the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, in its report which was published as a proposed regulation in the **Federal Register** of November 2, 1979 [44 FR 63274], states:

> To supplement mechanical removal of offending agents, a number of chemical agents claiming usefulness for prevention of plaque, calculus, or gingivitis are presently under investigation. The potential value and safety of these agents, which include quaternary ammonium compounds, enzymes, organic fluorides, and various antibiotics, have not been conclusively ascertained. The specific antimicrobial compounds for which some success is claimed in clinical studies include several agents. Among them are cetylpyridium chloride and combinations of cetylpyridium chloride and domiphen bromide which achieved a 30- to 40-percent reduction in dental plaque (Refs. 7 and 8). Other potentially effective agents include thymol and eucalyptol (Ref. 9), alexidine (Ref. 10), peroxides (Ref. 11), chlorhexidine (Ref. 12), and an investigational compound CC10232 (Ref. 7). A major concern in the use of these agents is their tendency to disrupt the normal microbial ecologic balance of the host (Ref. 13).

After considering these ingredients and the theories and rationale proposed for the effectiveness of drugs used for prevention and control of plaque and gingivitis, the [Dental] Panel has concluded that such approaches are at present so controversial that there can be no general recognition of the effectiveness of these agents for these indications at this time.

The [Dental] Panel, therefore, recommends that all claims stating or implying prevention, control, or treatment of plaque or gingivitis be placed in Category II and further recommends that antiplaque and antigingivitis agents be investigated and approved through the NDA process.

Additionally, the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products stated at 44 FR 63283 that:

> The [Dental] Panel concludes that drug products which have antiplaque, plaque control, or gingivitis claims are not currently appropriate for the OTC market because there is no general recognition of any such drug products as safe and effective for these indications at this time. Accordingly, the Panel recommends that such drug products and claims should be evaluated by FDA through the NDA procedure.

The rationality of plaque reduction, as a criterion of effectiveness for antimicrobial agents that are used in the mouth and throat, is highly debatable and evidence of the validity of the method is scant. There was considerable discussion of this issue in the deliberations of the Panel and in making its final determination the Panel relied upon the opinions of consultants and statisticians who are experts in this field of endeavor, in addition to relying upon the expertise of the Panel. At the January 4, 1979 meeting of the Advisory Review Panel on OTC Oral Cavity Drug Products, Dr. S. S. Socransky, Dr. W. H. Bowen, and Dr. F. B. Engley were invited as consultants to present their views on plaque reduction.

In his presentation, Dr. Socransky stated:

> What does the particular [antimicrobial] agent do? What is it active against? If you are cutting down microorganisms in the oral cavity, which I gather is the claim of this particular agent, then precisely what is the effect of cutting down these microorganisms in the oral cavity? Does it have some effect on microbial infection, bites, and things like that, or does it have an effect on dental caries, periodontal disease, or anything else? Or is it merely an effect on bacterial infestation just accumulations of organisms in the mouth?
>
> I do not think from the evidence that we have seen that you can go beyond making the claim at this moment that this is cutting down the numbers of organisms in the mouth temporarily. It is not clear that this is cutting down infections of the oral cavity, such as those induced by bites or something of that type, nor is it clear to me, at any rate, that it has an effect on caries, or periodontal diseases of any type in any striking fashion.
>
> When one cuts down the bacterial plaque, or any bacterial accumulations on tooth surfaces, I am not sure which organisms are influenced by anything that I have seen so far, and it could be possible that one is cutting down on harmful microorganisms, which is certainly reasonable.
>
> It is equally possible that somebody is cutting down on organisms that are potentially beneficial.
>
> So to clarify this role, I think that despite some of the concerns with some of the statistical handling of the information there is a cutdown in bacterial plaque to a degree. The amount that is reduced varies from very little to a great deal, depending on the study one reads.
>
> The significance of this in terms of beneficial effect, which is apparently what the public is after, is unclear to me.
>
> What has been used has been an area measurement, primarily, in the index—a weight measurement in terms of wet weight. There have been few, if any, that I have read of, actual measurements of numbers of microorganisms.

Dr. Bowen continued the presentation by stating:

> The question that [Dr. Socransky] has also raised is that even if we accept that there is an antimicrobial effect which results in the production and formation of plaque by a certain percentage, I am unclear what this means to a patient or subject who uses.
>
> Plaque is not a disease. It is probably a potential disease-producing entity. Its presence does not invariably result in disease; and, while there may be reasons for simply removing dental plaque, certainly I would think that the general public believes that if they had a small percentage in reduction of plaque, they might, in fact, have a reduction in disease. That is not necessarily so.

Dr. Engley stated that reduction of plaque is an unclear term:

> When you say reduction, you are talking about size and weight, but you are not talking about the numbers of organisms in the plaque. Sometimes you can reduce the glucan or the capsular material or the envelope material and come out with the same number of organisms but lower volume and lower weight.

Statistical data relevant to antimicrobial activity were submitted to the Panel and subsequently reviewed by a consultant statistician at the request of the Panel. The following is a summary of his comments:

Data have been presented which indicate effectiveness of domiphen bromide, the combination of CPC [cetylpyridinium chloride] and domiphen bromide, and the combination of menthol, thymol, eucalyptol, and methyl salicylate. The effectiveness relates to plaque reduction as measured by the Quigley-Hein index or the Turesky modification on the Quigley-Hein index. This index measures surface area of plaque. Before an antimicrobial claim is appropriate it must be established that the reduction in the Quigley-Hein index correlates with an antimicrobial action. None of the studies mentioned above attempt to do this. The claim that appears to be appropriate given the above studies is a claim dealing with surface area of plaque within a 7- to 21-day period.

The Panel, therefore, does not regard as valid and has not accepted data on

effectiveness of antimicrobial agents in oral health care products for treating sore throat and sore mouth based upon their ability to inhibit plaque formation.

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7. *Oral malodor.* Oral malodor, also commonly known as "bad breath," "foul breath," or "halitosis," is not new or exclusive to modern times, nor is the plethora of preparations used to overcome it. Through the ages, attempts at elimination or masking of oral malodor have ranged from the chewing of odoriferous substances such as berries, perfuming, administration of enemas, smoking flavored cigarettes, and tongue scraping, to the more recent practice of instituting hygienic measures using various cosmetic preparations, such as odoriferous mouthwashes and gargles, and lozenges. Some of the products employed contain antimicrobial and other active ingredients for which therapeutic claims are made in addition to cosmetic claims.

The universal prevalence of oral malodor indicates that to have some degree of malodor is a normal human trait and is not evidence of the existence of any pathologic state. The assumption that oral malodor is associated with certain diseases states is scientifically incorrect. The presence of oral malodor is not indicative of the existence of systemic or oral disease and of the need for unsupervised self-treatment with medicated products. Ketone-like breath of diabetes, which is sweet and pleasant, is not a true oral malodor. In much of the older medical literature, associations between oral malodor and certain systemic diseases generally have been established in hospital environments. Since such an environment does not necessarily assign much importance to oral hygienic measures, it is not surprising that many hospitalized patients may manifest foul breath irrespective of the disease for which they are confined.

Since very few, if any, individuals can self-determine whether they have oral malodor (Ref. 1), the fear that failure to promptly institute medicated mouthwash usage may delay the treatment of a serious disease entity is unfounded. Unless a social contact informs an individual that he or she has malodor, the individual may be unaware of its presence. The presence of malodor ordinarily is not indicative of the existence of a pathologic state and results in no physical harm to a subject.

The Panel concludes that claims in the labeling of many oral health care products intended to overcome mouth odors are therapeutic claims and that most mouth odors are not associated with symptoms of pathologic processes requiring the need for medicated oral health care products. It is obvious that there may be differing opinions on this point between a product's sponsor and the Panel. It is the consensus of the Panel, therefore, that a detailed discussion of oral malodor should be a part of this document. The reason for this is so that the facts and reasoning upon which the Panel's recommendations concerning the use of products for suppression of malodor are based will be understood and recorded.

a. *Factors causing oral odors.* Oral odors can be classified according to their source. They may arise from systemic or local (i.e., nonsystemic) conditions or a combination of both. Both the systemic and local conditions can be due to internal (intrinsic) or external (extrinsic) causes. Examples of intrinsic systemic causes are the ketonic breath of diabetes mellitus, the urine-like malodor of uremia, and suppurative processes of structures of the upper and lower air passages and lungs. Examples of causes of extrinsic systemic malodors include ingestion of onion, garlic, wines and other alcoholic beverages, volatile drugs, and other odoriferous substances. The term "oral malodor" is nonspecific and ordinarily implies that the mouth odor is unpleasant and offensive, irrespective of etiology. Not all mouth odors are necessarily unpleasant and a distinction should be made between those that are offensive and can rightfully be classed as malodors and those that are not.

The frequency with which mouth odors due to systemic diseases appear in the population at large is dependent on the frequency of occurrence of the disease states that produce them. The frequency of these odors could perhaps be estimated from epidemiological data. Diabetes is one of the more common systemic diseases which can taint the breath with a sweet odor, since it is due to the exhalation of ketones. The odor is not necessarily unpleasant and offensive. Other systemic disease states, such as uremia, which is accompanied by a urine-like oral breath odor, and suppurative broncho-pulmonary diseases, are relatively less common. A sweet-smelling breath, or a urine-like breath, is, therefore, not a typical oral malodor. Odor resulting from suppurative pulmonary diseases can be disagreeable and offensive and classed as a malodor.

It should be noted that persons who have mouth odor due to systemic diseases are generally aware of their disease state. Also, the appearance of mouth odor is not the first symptom of that disease state but generally ensues after the disease is established or appears simultaneously with the major disease symptoms. To the Panel's knowledge there is no plethora of reports in the medical and dental literature of any significant number of cases in which mouth odor was an early diagnostic sign that established the presence of a systemic disease entity.

The concept that stomach odors taint the breath is false. The esophagus is a collapsed tube that communicates with the oral cavity only during swallowing, belching, or regurgitation (Refs. 2 through 7). Normal lung air does not contribute to mouth odors except in smokers or in those who have consumed alcoholic beverages or ingested

odoriferous foods such as garlic or volatile drugs such as paraldehyde that yield volatile byproducts which are excreted by the lung (Ref. 8). The contribution to oral odors by systemic conditions is minimal. A review of the literature indicates that more than 90 percent of all oral malodors are due to local oral conditions in the mouths of healthy persons (Refs. 3, 4, and 9). The remaining 10 percent of cases are due to extraoral causes of nonpathologic origin. Of these, most of the odors are due to volatile aromatic compounds circulating in the blood that are excreted into the lung air (Refs. 9 and 10).

It is estimated that upon arising in the morning, at least 9 out of 10 persons have oral malodor. Reilly (Ref. 5) has written, "Following sleep, nearly everyone has an unpleasant breath. The reduced activity of the tongue and the cheeks, together with the reduction in the flow of saliva, allow the bacterial flora of the mouth to be more active, resulting in an unpleasant breath."

In the past, substances causing oral malodors have been incorrectly assumed to consist of amines, fatty acids, and indoles (Ref. 11). By use of the gas chromatograph, a highly sensitive instrument capable of detecting various volatile substances to parts-per-billion ranges, it has been established that deadspace gases of the malodorous mouth consist mainly of minute traces of highly odoriferous volatile sulfur compounds. The most common and abundant of these are hydrogen sulfide, and methyl mercaptan. Traces of dimethylsulfides are also found (Refs. 12 through 15). The presence of volatile sulfur compounds detected by using the gas chromatograph has been correlated with the presence of nose-perceptible oral malodorous substances in test subjects. For example, if the subject had nose-perceptible oral malodor, the chromatograph showed the presence of volatile sulfur compounds. Absence of nose-perceptible malodor was accompanied by the absence of volatile sulfur compounds (Ref. 16).

Studies performed on the supernatant fluid of saliva, salivary sediment, and plaque have shown that microorganisms, in the presence of appropriate substrates, produce volatile sulfur compounds (Ref. 14). Sterile saliva has been shown not to produce putrefaction (Ref. 17) and malodor. The amines and indoles present have been shown to be nonvolatile, nonodorous substances. Volatility of a compound is a sine qua non requirement for its detection as a mouth odor causative agent (Ref. 11). The Panel, however, finds no data that support the concept that traces of volatile sulfur compounds formed by the resident oral flora in mouths of healthy persons are deleterious and injurious to the health of the individual. Likewise, it finds no data that justify a therapeutic use of antimicrobial agents for suppression of the formation of volatile sulfur compounds and other substances causing malodor.

b. *Role of microorganisms in the production of mouth odors.* The body has no mechanism for producing volatile sulfur compounds. Mammalian cells apparently do not possess the metabolic machinery (enzymes) to elaborate volatile sulfur compounds. Consequently, the production of volatile substances responsible for malodors in humans is dependent largely upon microbial metabolic processes. Reports of investigations have shown that microorganisms play an essential role in the production of oral malodor (Refs. 17 and 18). The incubation of sterile saliva produces no malodor. Yet, when whole nonsteril saliva is incubated, a shift of the bacterial population from gram-positive to gram-negative occurs with attendant malodor production (Ref. 18). However, these microorganisms are part of the indigenous oral flora and are known to be nonpathogenic under ordinary circumstances.

An important metabolic characteristic of certain gram-negative microorganisms found in the mouth is their ability to produce volatile sulfur compounds. One species of microorganism with pronounced metabolic capabilities to produce volatile sulfur compounds is fusobacterium, although other species such as peptostreptococcus may also be involved. All of these microorganisms are anaerobic and thus exist in areas of the mouth where the oxidation-reduction potential favors their survival. The principle areas where this occurs are the gingival crevices, interdental spaces, tonsilar folds, and the interpapillary crypts of the tongue (Ref. 17). The tongue has long been implicated as a reservoir of malodor-producing bacterial flora (Refs. 1 and 19).

It has been shown that glucose does not favor the production of malodor in incubated saliva (Refs. 17 and 20). Glucose, like other carbohydrates, favors fermentative metabolic pathways which produce nonodoriferous organic acid end-products. Amino acids, especially those containing sulfur, and short-chain peptides composed of sulfur-containing amino acids are the substrates leading to maximal putrefactive processes by the gram-negative microorganisms.

There are many reports of studies, both controlled and uncontrolled, on the etiology of local oral malodor. Most of these point to gram-negative organisms as the causative factors. In a 1949 study conducted by Morris and Read (Ref. 21), the use of a dentifrice, mechanical tongue prophylaxis, and an antibacterial mouthwash were found to be effective in reducing oral malodor. Water rinsing, however, was ineffective. However, this finding is not in agreement with findings found in other studies that indicate that water rinsing can be effective (Refs. 22 and 23). The antibacterial mouthwash used in the study of Morris and Read produced longer-lasting breath protection than tongue prophylaxis or brushing with a dentifrice. It was also noted in this study that the masking effect produced by flavoring agents contained in the mouthwash or dentifrice did not last, or mask, for more than 20 minutes, even though the protection against malodor continued for 3 hours following mouthwashing and 2 hours following toothbrushing.

c. *Elimination of mouth odors.* The control of local oral malodor depends upon its cause and may be accomplished by one or more of the following measures: purging, masking, neutralization, or bactrial inhibition. These measures are effective in controlling malodors of local origin and are generally not of value in controlling mouth odors of systemic origin, i.e. "onion" or "garlic breath."

(1) *Purging.* Malodors can be purged temporarily from the mouth by rinsing with water, brushing the teeth, using dental floss, or by eating a meal. The malodors are eliminated completely in some cases, reduced for a short time period in others, and in some cases not affected at all. The purging is due to a physical rinse-out or dislodgement of accumulated volatile sulfur compounds, food debris, or stagnant saliva, or to a reduction in the numbers of bacteria in the mouth. Dilution effect is common to most liquid preparations or products used to attempt to eliminate malodor.

(2) *Masking.* Local oral malodors may be masked by introducing a new, more pleasant odor into the mouth. This masking effect usually lasts only as long as the masking agent remains in the mouth at perceivable levels, generally from 15 ot 20 minutes in duration (Ref. 21).

(3) *Chemical neutralization.* Some agents react chemically with malodorous volatile compounds and form insoluble nonodorous products, usually nonvolatile sulfides. Chemical

neutralization is dependent upon how long the neutralizing agent lingers in the mouth, the quantity of malodorous material to be neutralized, and how quickly the malodor-causing chemicals are being remade. Chemical neutralization provides a longer-term local antimalodor effect than purging or masking. It may be prolonged further if accomplished by bacterial inhibition.

(4) *Bacterial inhibition.* Because certain strains of bacteria may cause oral malodor, inhibiting their metabolism or enzymatic activity or killing them may result in a temporary deodorizing effect. A longer term of action is apparent when the malodor is due to bacterial action and an antimicrobial agent is used. The effect persists even after the effects of purging and masking have been dissipated if they have also been used simultaneously. (Ref. 21). However, after meals and overnight sleeping the bacteria, having been mostly inhibited, will usually return to their original numbers and metabolic activities.

Because oral malodor is caused mainly by gram-negative anaerobes, only antimicrobial ingredients known to be effective against the causative organisms are effective in suppressing the malodor. However, agents that may be effective in one person may not be effective in another due to variations in the susceptibility of the microorganisms to the agent. Theoretically agents which preferentially inhibit or kill gram-negative anaerobes should be more effective in controlling oral malodor. Whether or not this is always the case is not known. There is ample evidence that the microbicidal effects of the antimicrobial agent are partial and incomplete and all the microorganisms are not killed by one application of the antimicrobial agent. The malodor due to bacterial action returns after the antimicrobial agent loses its effect and the microorganisms again begin to proliferate. In order to obtain a sustained effect, the user would have to reapply the ingredient repeatedly over 3- or 4-hour periods as long as the malodor persists (Ref. 21). The Panel does not consider this a judicious practice and does not recommend the unsupervised use of medicated oral health care products, particularly those containing antimicrobial agents, when there are no symptoms and when there is no evidence of the presence of a pathologic process. The Panel emphasizes that mouth odors without the presence of symptoms are not indicative of the existence of pathologic states and the use of antimicrobial and other therapeutic agents for their elimination is unwarranted.

d. "*Malodor testing.*" Various techniques have been divised for malodor testing. Although there may be variations among the techniques depending upon the subject population, investigators, location, purpose of the study, etc., most "malodor tests" follow a similar general protocol. Mouthwash formulations intended to control local oral malodor are tested in populations composed of normal subjects. Since most subjects exhibit oral malodor early in the morning and before the institution of hygienic measures, testing is done at this time. The subjects rinse with a mouthwash or a water rinse as a control. Expert judges, selected for their ability and consistency in scoring the intensity of oral malodor according to a pre-determined scale, sniff the breath of the test subjects before rinsing and at selected time intervals thereafter. The results are then analyzed and compared with effects of the water control rinse. Such testing is useful for demonstrating the relative effectiveness of a mouthwash compared to a water control rinse, the time period during which the mouthwash protects the oral cavity against oral malodor, and the relative pleasantness or unpleasantness of the subjects' breath before and after rinsing. Obviously such testing is in no way related to testing of the effectiveness and safety of a product for treatment of symptoms of pathologic processes causing sore mouth or sore throat. The Panel is unaware of any valid data concerning the relationship between sore mouth, sore throat, or both, and the presence or suppression of oral malodor. The "malodor test" is included in this discussion merely to indicate that such a test is in use primarily for evaluation of cosmetics and that the Panel considers it of little or of no value in the evaluation of antimicrobial or other therapeutic activity of oral health care products used to treat sore mouth, sore throat, or both.

The concept that some microorganisms present in the oral flora may play a beneficial role and help maintain a healthy state of the mouth has not, to the Panel's knowledge, been propounded, but certainly merits mention and consideration in this document. It is not out of the realm of possibility that certain nonpathogenic microorganisms play a contributory role in the self-cleansing process with the oral cavity is naturally endowed. Should this be the case the elimination of these microorganisms with medicated products would indeed be irrational.

In summary then, a review of the literature and the Panel's experience in laboratory and clinical research on oral malodor supports a local, oral origin for most oral malodors. In the majority of cases, the odors are due to traces of highly odoriferous, volatile sulfur compounds. These compounds are elaborated by the resident bacterial flora in the mouths of health persons. The microorganisms that have the metabolic pathways to elaborate volatile sulfur compounds in the oral cavity are mostly of the gram-negative nonpathogenic anaerobic variety. No relationship between the presence of these gram-negative organisms in the mouth and throat and diseases causing sore throat and sore mouth or other local or systemic diseases has been established. Normal lung air does not contribute to true oral malodor of local origin nor does the gas in the stomach. The stomach, for anatomic and physiologic reasons, is closed to the oral environment, except during swallowing and belching. The Panel considers products intended for elimination or suppression of mouth odor of local origin in healthy persons with healthy mouths to be cosmetics unless they contain antimicrobial or other drug ingredients. The Panel is mindful of the fact that the Federal Food, Drug, and Cosmetic Act indicates that articles that are cosmetics, but which are also intended to treat or prevent disease or to affect the structures of the human body, are drugs as well as cosmetic and must comply with both the drug and cosmetic provisions of the law and regulations (Ref. 24). Claims for the suppression of mouth odors using medicated oral health care products that are linked to a drug action, i.e. antimicrobial action, are drug claims. The Panel considers such drug claims to be Category II drug claims.

It is the consensus of the Panel that the use of OTC mouthwashes to control oral malodor is simply determined by an individual's need for social acceptance or personal oral gratification and is not mandated by the need to relieve symptoms of a pathologic state.

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8. *Quaternary nitrogenous cationic antimicrobial agents.* The quaternary nitrogenous cationic agents manifesting antimicrobial activity evaluated by this Panel fall into several principal chemical groups.

a. *The quaternary ammonium compounds.* In these, the four hydrogen atoms of the positively charged ammonium ion are replaced by various organic radicals. The trivalent nitrogen atom of ammonia is converted to a pentavalent state capable of forming four covalent bonds and one positively charged ionic bond; the process is referred to as quaternization. These derivatives form bases which, when dissolved in water, yield a positively charged quaternary-substituted ion and a hydroxyl ion. These bases form salts with various acids, the most common of which in OTC products are hydrochloric and hydrobromic acid. When dissolved in water, hydrochloride or hydrobromide salts derived from substituted ammonia yield a positively charged ammonium ion and a negatively charged chloride or bromide ion. The cation manifests the antimicrobial properties. Benzethonium chloride is an example of such a compound.

b. *The pyridinium compounds.* In the pyridinium compounds the trivalent nitrogen atom in pyridine is converted to a pentavalent state with four covalent bonds and a positive ionic bond. When dissolved in water, a base forms which ionizes into a pyridinium ion and an hydroxyl ion. As is the case with substituted ammonium derivatives, the bases form salts with acids, usually hydrochloric or hydrobromic acids, and these are referred to as "pyridinium salts." The salts ionize into a pyridinium ion, which is positively charged, and a chloride or bromide negatively charged anion. Cetylpyridinium chloride is an example of such a compound. The hydrogen atom on the nitrogen atom of the positively charged pyridinium ion is substituted by an aliphatic (straight chain) or aromatic (benzene ring) radical. The cation manifests antimicrobial activity similar to the quaternary ammonium ion.

c. *The quinolinium compounds.* In these, the trivalent nitrogen atom of quinoline is converted to a pentavalent state to form quinolinium derivatives. Substitutions with aromatic and aliphatic radicals may be made on the nitrogen atom as is the case with the ammonium and pyridinium derivatives. A methyl group on the 2 position of the quinoline nucleus yields a series of derviatives, called quinaldinium derivatives, when the nitrogen atom is quaternized. Quinaldinium is a base that dissolves in water to yield the quinaldinium ion, which is positively charged, and a hydroxyl ion. the quinaldinium bases form salts with acids which ionize into the quinaldinium ion and an anion. Dequalinium chloride is an example of an antimicrobial agent evaluated by the Panel falling into this category.

These three types of compounds all have one characteristic in common, i.e., they have one or more "quaternary" nitrogen atoms in their structures. For this reason, they are frequently called "quats." Many of them reduce surface tension and manifest various degrees of antimicrobial activity. The chemical behavior and biologic activities of the ammonium, pyridinium, and quinaldinium compounds are similar in most respects, so much so that some clinicians fail to make a distinction between the various types of compounds and refer to all of them as "quaternary ammonium compounds." All form salts with hydrochloric or hydrobromic acid, as does ammonia, and all salts are ionized when dissolved in water into "quaternary" nitrogenous positively charged cations and anions. The ability to substitute various organic radicals on the nitrogen atoms allows for the synthesis of a large group of variants. A large number of these variants has been prepared and tested for antimicrobial activity. The number that is clincially useful, which has been prepared from the large number of variants, is small. This Panel has evaluated only benzalkonium chloride, benzethonium chloride, cetyl benzalkonium chloride, domiphen bromide, cetalkonium chloride, and dequalinium chloride.

The nitrogenous cationic agents are characterized by a structural balance between one or more water-repelling (hydrophobic) groups and one or more water-attracting (hydrophilic) groups. It has been shown in the case of the substituted ammonium derivatives that in order to have pronounced antimicrobial activity one substituent must be a long alkyl (straight chain) radical of 12–16 carbon atoms, one substituent must be one short aromatic substituted alkyl group (a benzene ring on a short straight chain of several carbon atoms), and the remaining substituents must be two alkyl groups (straight chain of one or more carbon atoms such as methyl or ethyl groups). The long carbon chain may be modified by adding aromatic groups or hydrogen atoms. The long carbon chain confers lipophilic-hydrophobic properties and acts in a manner similar to a fatty acid. It is hydrophobic and oriented into a lipid phase of a water-lipid interphase.

The nitrogen atom is postiviely charged, hydrophilic, oriented into the water phase of a lipid-water interphase, and it acts like an ammonium ion. The pyridinium and quinolinium derivatives, likewise, have hydrophobic-lipophilic groups by virtue of their aromatic structures. They also have a long carbon atom chain substituted for a hydrogen atom on the nitrogen atom and a hydrophilic group that results from the ionic activity of the quationized nitrogen atom. Thus, all three types must have one fatty-acid type of radical as a substituent on the nitrogen atom.

The quaternary nitrogen cationic derivatives are capable of altering the physiochemical relationships of liquid-liquid or gas-liquid interphases. Some cause a marked reduction of surfaoe tension. In some cases the surface tension is reduced to as low as 37 dynes per square centimeter (dyn/cm$^2$) at 25° C. Substances that act in this manner are also referred to as "detergents" or "surface-active" compounds.

These compounds have characteristics that are common to the entire class of quaternary nitrogenous derivatives. The exact mechanism by which quaternary nitrogenous compounds exert their antimicrobial activity is not known. A number of mechanisms of action have been suggested: (1) They may exert their antimicrobial activity by disrupting the microbial cell membrane and allowing the microbial cytoplasm, enzymes, or other substances to diffuse out of the cell; (2) they may act by dissolving the protective lipid films in the microbial cell membranes, since they are lipophilic; (3) they may act by denaturing certain proteins with which they combine on the surface of a cell; (4) they may inactivate microbial intracellular enzymes; and (5) they may interfere with the activity of enzymes involved in the transport of chemicals across cell membranes. Any one of the above or a combination of two or more mechanisms may be responsible for the antimicrobial activity. The cells of the host can also be affected by these substances, as is the case with other antimicrobial agents, but available data indicate they do so to a lesser degree in most cases. There is no well-defined correlation between the surface-tension-reducing activity of these compounds and their antimicrobial activity. Many substances that cause a pronounced decrease in surface tension possess no significant antimicrobial activity. The quaternary nitrogenous agents manifest a high degree of absorbability. They are readily absorbed by activated charcoal, silica gel, and to a lesser degree, by agar and other absorbents. A similar degree of absorbability is believed to occur on the cell surface, altering metabolic activity.

The antimicrobial activity of quaternary nitrogenous agents is due to the aforementioned physiochemical attributes. On the other hand, these same attributes also account for the inactivation of quaternary nitrogenous agents and cause them to be ineffective. They are readily absorbed or acted upon by other agents present in an infected area, wound, or culture medium. They are inactivated by proteins, pus, debrided cells, blood, rubber, cotton, wool, and even glass, plastic, and other substances capable of absorbing them. Soaps, in particular, since they are anionic detergents, deactivate quaternary nitrogenous compounds when only small traces are present. The anionic antimicrobial agents cannot be formulated with the cationic agents since each type deactivates the other. In addition, their activity is dependent upon environmental temperature and pH. They are ineffective at near-neutral pH but their activity is increased as pH increases. Many manifest their greatest activity at a pH 8 or above. This is a greater pH than that of the tissues. The pH of tissue fluids in infected areas is usually acidic and ranges from 5 to 7. The antimicrobial activity increases as environmental temperature increases.

The majority of quaternary nitrogenous compounds are bacteriostatic rather than bactericidal. They are more active against gram-positive bacteria than gram-negative organisms. This particular attribute of variation in antimicrobial activity casts doubt on their value and effectiveness as antimicrobial agents in the mouth and throat where gram-positive bacteria abound. The "quats" are nonspecifically absorbed to the cell membrane and the unprotected cell menbrane is more sensitive to their action than the protected cell membrane, which probably accounts for differences in sensitivity. The differences in sensitivity between gram-positive and gram-negative organisms is probably due to greater absorbability of the "quats" to the gram-positive organism and the ability of the agent to pass into and beneath the cell wall of the gram-positive microorganism.

Strains of *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* are particularly resistant to these antimicrobial agents. Most bacterial spores remain viable even after prolonged contact with solutions of quaternary nitrogenous compounds. Their usefulness in combating fungal infections has not been established. The fungicidal activity of the "quats" is less than their bactericidal activity. Most of the quaternary nitrogenous derivatives of this type are not virucidal. When they are used as skin disinfectants, some form a film on the skin under which bacteria remain viable.

Cationic agents appear to possess a low order of systemic toxicity in animals and humans. Poisoning from oral ingestion has been reported. The toxicity reported appears to be related to the surfactant nature of the "quats." Rabbits can tolerate 1.2 cubic centimeter (cm$^3$) of a 1-percent benzalkonium chloride solution subcutaneously or intraperitoneally for days without signs of adverse effects. Chronic toxicity studies or various compounds in animals reveal weight loss, loss of appetite, etc. Prolonged contact with the skin and mucous membranes produces irritation. In rabbits, the highest concentration of benzalkonium chloride that could remain in contact with the skin for 24 hours without signs of irritations was 0.1 percent. The concentrations in which the "quats" are used are low so that irritation usually is not a serious problem. As is the case with other agents, the "quats" can bind with protein and act as haptenic antigens and produce sensitization. However, this has not been a common occurrence and the incidence of sensitivity reactions has been low.

The safety of quaternary nitrogen compounds for use in the oral cavity is difficult to evaluate because the available data concerning application on the mucous membranes of the mouth and throat is scant. Data from controlled studies on the permeability through the membranes, the degree of systemic absorption, degree of irritancy, and sensitizing potential after application to the oral mucous membranes are not available, and a definitive judgement cannot be made at this time. Data on absorption through the mucous membranes, blood levels, and biotransformation likewise are not available. Toxicity studies have generally been limited to animal species; little data are available on the effects of chronic use on people. Controlled clinical toxicity studies are, in most cases, lacking. There is a need for additional data on irritation and sensitization from chronic exposure on the oral and pharyngeal mucous membranes in order to properly evaluate these ingredients, particularly with regard to safety.

The quaternary nitrogenous compounds are ionized. Ionized substances are not readily absorbed

through the lipoid barriers of the cell nor do they penetrate the blood-brain barrier; therefore, one would expect these compounds not to be absorbed in any great quantity. On the other hand, to what degree the lipophilic pole present on the molecule enhances their lipid solubility and adsorbability is not known. Were they not soluble, they would not penetrate the cell of the microorganisms or cells of the host. Quaternary nitrogenous compounds, if absorbed, could act as automatic ganglionic blocking agents. They may also manifest a curariform action. It has been suggested that a possible use for certain of these compounds would be as ganglionic blocking agents. Another possible use suggested is as anticholinergic agents. The quaternary nitrogenous compounds manifest no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

Effective cationic agents have the following advantages over other antimicrobial agents for use as antiseptics: (1) They are used in relatively low concentrations and are nonirritating to tissues in such concentrations: (2) they have a rapid onset of action; (3) they "wet" and penetrate tissue surfaces quickly and readily; and (4) they possess detergent emulsifying and keratolytic actions.

This disadvantages are (1) they are irritating in high concentrations; (2) they vary in the spectrum of antimicrobial activity; (3) they are inactivated by anionic agents, proteins, various adsorbents, etc., (4) data on toxcity, both local and systemic, and acute and chronic, in humans are scant; (5) the in vitro data do not correlate with and provide an index of in vivo effectiveness; (6) they are of limited use as virucidal and fungicidal agents; and (7) little is known of their actions on protozoan type organisms.

9. *Volatile oils.* A group of oils, obtained from botanical sources often referred to as ethereal of essential oils, contains a miscellaneous number of ingredients that have been used for therapeutic purposes. They have been used empirically and are considered to be effective antimicrobial agents in spite of inadequate data to support this contention. The volatile oils are mixtures of various types of chemicals whose composition is inconsistent and varies with their source. For this reason, a general statement is made here concerning volatile oils.

The volatile oils are obtained from various plants by distillation or by pressure. They are found in different types of fruits or flowering parts of plants, all of which are widely distributed throughout the plant kingdom. They are not obtained from one single source. Most are strongly odorous and, therefore, are used as perfumery to conceal disagreeable odors and tastes in medicine. They must be distinguished from the fatty or fixed oils which are nonvolatile.

Most volatile oils are mixtures that have terpenes as their commonest constituents. Some oils contain only terpenes, depending upon the source. Terpenes are hydrocarbons of the aromatic series that possess the general formula $(C_5H_8)_n$. Some terpenes are combinations of dihydrobenzene with propyl and methyl groups and at least a dozen terpenes of this type are known. Another group of hydrocarbons found in these oils is known as the sesquiterpenes, while a few are diterpenes. Some volatile oils consist of these hydrocarbons exclusively, but most of them contain some oxidized aromatic substances such as phenols, ketones, aldehydes, acids, and components of these substances. For instance, some contain camphor, thujone (from oil of absinthe), sabinol oil, safro, thymol, eucalyptol, myristicine, and vanillin.

Many of these oxidized products crystallize out when the volatile oils are cooled or are left standing. The resulting solids are known as stearoptens, while the remaining fluid is called eleopten. The constitutents of the oils that contain oxygen in their molecular structures are not as volatile as the pure hydrocarbons. The odor is due mainly to the oxidized substances. A few oils contain nitrogenous bodies, generally in the form of cyanides. On the other hand, the majority of volatile oils obtained from the curuciserae species contain sulfur bodies which give them a pungent, disagreeable odor quite different from that of the other oils.

The volatile oils are generally clear, colorless liquids, although some are green or blue in color. After long standing they may become discolored, decompose, and become acidic in reaction resulting from the formation of resins. Some are light, sparking fluids. Many of the plants from which the volatile oils are obtained possess other active constitutents, such as bitters. Many of the preparations used in therapeutics are formed not from the distilled oils but from crude parts of the plants. In many cases, the oil is not the only active principle present in the plant.

Strong solutions of volatile oils have a hot, burning taste and if kept in the mouth cause redness and irritation of the mucous membranes, although some of them induce a sense of coolness at first. At the same time the organs of smell are affected by these oils because most possess characteristic odors. Irritation of the mouth leads to reflex secretion of saliva which is often very profuse. When used in the mouth or elsewhere the antiseptic action of the oils may have a beneficial effect in some conditions.

In the stomach the oils cause the same sensation of warmth. The appetite may often be increased and the feeling of distension after meals is often relieved. Some cause the release of quantities of gas. Substances which produce these in the stomach are known as carminatives, and many explanations of their action have been offered. In the intestines small quantities generally increase movements while larger quantities decrease them. Sometimes the bowel is relaxed due to reflexes arising from interaction of the oils on the stomach. In practice, they often relieve intestinal flatulence and distension and lessen the spasms which cause colic.

Many of the terpenes are oxidized to phenols in the body and then excreted in the urine. For the most part, they combine with glucuronic acid and sulphuric acid. They leave by way of the expired air and impart an odor to the breath. In the course of excretion, some of the oils may cause irritation of the lungs. Some of the oils are employed as expectorants to increase bronchial secretions.

The volatile oils all possess some antimicrobial activity which is believed to be due to their volatility and solubility in liquids. This enables them to penetrate readily into the protoplasm. Many of them appear to be more germicidal than phenol under favorable circumstances. They are generally too insoluble in water to be employed easily for medicinal purposes, and this also limits their usefulness as antimicrobials in the highly aqueous environment of the mouth. When some are applied to the skin they cause redness, itching, and warmth resulting from local dilation of the vessels. This dilation may be due to penetration of the oil into the cutaneous arterioles, veins, or to local reflex effects from the irritation of the terminal sensory nerves. When painted on the mucous membranes, such as those of the eye, nose, or on wounds, the volatile oils cause a similar type of irritation which is characterized by redness, congestion, and smarting. Some are used as counterirritants on the skin. The Panel does not believe that the counterirritant effect is of any therapeutic value on the mucous membranes. It is the consensus of the Panel that individual pure ingredients such as thymol, eucalyptol,

and menthol extracted from the volatile oils are more effective, safer, and are more easily evaluated than these heterogenous mixtures of inconstant composition. The Panel feels that the volatile oils may be used as flavorants or to impart pleasant odors to a product.

10. *Absorption, distribution, and metabolism.* In addition to their local cytotoxic effects, many topically applied antimicrobial agents and disinfectants may manifest systemic toxic effects because they are absorbed from the mucous membranes, circulate in the blood, and affect susceptible target tissues and organs. Absorption readily occurs from the mucous membranes of the mouth, pharynx, and from the stomach, if these agents are swallowed. This has led to a further limitation of the use of certain effective antimicrobial agents. These systemic effects may not necessarily be due to the qualities which render such drugs antimicrobial. The systemic actions may be attributed to other pharmacologic or chemical properties of a drug. Systemic reactions may be avoided by exercising care in selecting a drug and by avoiding its misuse.

The manner in which an antiseptic is absorbed, its rapidity of absorption, distribution in the body, and systemic toxicity vary with each chemical and pharmacologic type and each individual compound. The mercurial derivatives, for example, are nephrotoxic; the chromates are likewise nephrotoxic; the phenols affect the central nervous system, etc. Antimicrobial agents, as is the case with most drugs, are metabolized by the liver or are excreted unchanged by the kidney if they are absorbed. Some are excreted into the intestine, particularly the colon. Some pass into the bile, and others pass into the sweat and into the milk of lactating women. The metabolic fate of each systemically absorbed drug is considered in the individual ingredient statements.

11. *Adverse reactions.* The adverse effects of antimicrobial agents contained in oral health care products merits consideration from two standpoints: (1) From the standpoint of short-term therapy when used to treat pathologic states that cause sore mouth and sore throat and (2) from the standpoint of long-term use for cleansing, elimination of mouth odors and other purposes when no pathologic state or symptoms of a disease exist. Most of the mouthwashes, rinses, and gargles evaluated by the Panel that contain antiseptics are recommended for long-term use on a daily basis or oftener. Some are used by consumers for years at a time. In many cases, there is a paucity of data on the remote adverse effects that may ensue from long-term use of these ingredients. It is the belief of the Panel that such ingredients should not be used until their safety, following chronic long-term use, has been established.

The general aspects of adverse reactions from use of all OTC oral health ingredients evaluated by the Panel have been discussed previously. (See part II. paragraph E. above—Adverse Reactions.) There are, however, certain specific aspects pertaining to antiseptics that have been discussed in a general manner in that section which require further discussion and elaboration.

Topically active antiseptics kill or inhibit the growth of microorganisms but are also cytotoxic and may injure normal cells of the host and cause tissue destruction. They may irritate tissues, be corrosive, and cause ulceration and even sloughing of the mucous membranes and submucosal tissues. These local, irritating reactions may occur during short-term as well as long-term use. Sloughing has resulted from the use of certain phenolic compounds, overuse of peroxides and other oxidizing agents, certain iodophors, and combinations of the volatile oils.

Recently, Bernstein (Ref. 1) has reported oral mucosal white lesions associated with excessive use of a commercial mouthwash. He found that the excessive topical application of a mouthwash containing 25 to 26.9 percent alcohol, thymol, eucalyptol, methyl salicylate, menthol, benzoic acid, and boric acid, at a pH of 4.4, produced asymptomatic diffuse white mucosal lesions in two patients. He concedes that any one or a combination of several ingredients in this mouthwash, as well as the acid pH or tonicity, must be considered as possible factors in the etiology of the white lesions. Alcohol is a likely suspect in view of a previous report by Baer and Archard (Ref. 2). Bernstein indicates in his discussion that several reports concerning the adverse effects of mouthwashes appear in the literature. He quotes two articles, one by Kowitz, Lucatorto, and Cherrick (Ref. 3) and another by Fisher (Ref. 4). In these reports it is noted that the most common adverse effect is a stomatitis due to a primary irritant effect or hypersensitivity. This adverse effect is manifested by erythema, ulceration, or ipithelial sloughing. Essential oils, astringents, and antiseptics are usually implicated in the etiology of these reactions. They occur as isolated cases in persons who have idiosyncrasies or who are sensitive to the preparations. They note that the acute symptomatic responses are not necessarily correlated with abuse of the product. The pathogenesis of this type of reaction appears to be different from the two reported cases in which prolonged contact of a chemical was associated with asymptomatic, nonallergic white lesions (Ref. 1).

Bernstein (Ref. 1) further states that very few articles have been published documenting white lesions associated with mouthwashes or ingredients contained therein. Although sloughing white patches following the use of chlorhexidine mouthwash was reported by Flotra and colleagues (Ref. 5), whom he quotes in this article, a subsequent study failed to reveal increased thickness of the stratum corneum in biopsy specimens taken from human subjects who rinsed with chlorhexidine (Ref. 6). In the cited article, Baer and Archard (Ref. 2) observed the development of white lesions of the gingiva and alveolar mucosa following the chronic and excessive topical application of isopropyl alcohol. Histologic sections revealed coagulative hyperparakeratosis and acanthosis. Discontinuation of the alcohol resulted in remission of the lesion. How many local reactions that never come to the attention of a manufacturer or sponsor of a product or the FDA will never be known because few physicians or dentists take the time or trouble to report the occurrence of such lesions, particularly if they disappear when use of a product is discontinued. The various types of lesions that have occurred and been reported from local effects of these ingredients are discussed in the description of the various ingredients.

Most ingredients in mouthwashes can be absorbed from the mucous membranes of the mouth or throat, or the stomach if swallowed. Ferguson, Geddes, and Wray (Ref. 7) recently reported that short-term therapy with a providone-iodine mouthwash had an adverse effect on 16 healthy individuals after 2 weeks of use. Significant increases occurred in the total serum iodide, protein bound iodine, inorganic iodine, T3 resin uptake, total thyroxine, and free thyroxine index. The possibility of thyroid suppression following long-term use is also mentioned in this article. The systemic effects from short-term therapy, as well as long-term use of antiseptics in oral health care products are mentioned, if known, in each ingredient section outlined below. In many cases, particularly in the case of the more recently introduced

antimicrobial agents, such as the quaternary nitrogenous compounds, there is a paucity of data on chronic systemic toxicity in humans.

Data on the tumorigenic, mutagenic, and teratogenic effects of antiseptics when used in oral health care products on a daily basis or more often for years at a time are sparse. There is some evidence that phenol may act as a cocarcinogen, but it has not been shown to do so conclusively. Phenol still is available for OTC use in mouthwashes, rinses, and sprays and will continue to be until additional data becomes available.

Weaver, Fleming, and Smith (Ref. 8) studied 200 patients with squamous cell cancer of the head and neck and compared them to patients in the general surgery group on use of tobacco, alcoholic beverages, and mouthwash. Analysis disclosed that patients with cancer of the head and neck used significantly greater quantities of tobacco and alcoholic beverages and mouthwash than the control group. However, 11 patients with cancer of the head and neck had abstained from alcoholic beverages and tobacco, but each had used significantly more mouthwash than had patients in the general surgery group. Several brands of mouthwash have an alcoholic content of 14 to 28 percent. Weaver, Fleming, and Smith (Ref. 8) feel the alcohol in the mouthwash may be a causative agent. They also indicate that other possibly irritating substances are contained in mouthwashes. These include cetylpyridinium chloride, thymol, eucalptol, phenol, methyl salicylate, and boric acid. Weaver, Fleming, and Smith (Ref. 8) quote Kowitz, Lucatorto, and Cherrick (Ref. 3) who have reported epithelial peeling, mucosal ulceration, gingivitis, and petechiae in as many as 25 percent of those dental and dental hygiene students who used 20 mL of full-strength mouthwash for 5-second intervals twice daily throughout a 2-week period. These signs of acute inflammation disappeared when use of the mouthwash was discontinued. Weaver, Fleming, and Smith (Ref. 8) feel that chronic irritation from use of mouthwashes may be carcinogenic. All but one of the previously mentioned 11 patients who developed cancer had used mouthwash several times daily for more than 20 years. Most of them used a brand of mouthwash that contained 25 percent alcohol. These data on the case histories presented in their report suggest that a history of the use of a mouthwash should be included for outpatients with premalignant or malignant lesions of the oral cavity, as mouthwash may indeed be carcinogenic for susceptible individuals. To their knowledge, no previous study has included a history of patients using mouthwash in the study of the incidence of cancer of the head and neck. Alcohol, in the absence of tobacco, appears to be a weak carcinogen. If a mouthwash is weakly carcinogenic, a susceptible person using this substance while abstaining from alcoholic beverages and tobacco might be expected to develop a carcinoma at a more advanced stage. Weaver, Fleming, and Smith (Ref. 8) also point out that it is interesting that 9 of 11 patients with cancer from excessive use of mouthwash were women and that all 11 patients had cancer involving the oral cavity. This is consistent with the site and distribution by sex for previously unexplained squamous cell cancer of the head and neck region reported from other sources by other clinicians.

Wlodkowski, Speck, and Rosenkranz (Ref. 9) have indicated that povidone-iodine is capable of specifically altering the deoxyribonucleic acid (DNA) of living cells and inducing mutations in salmonella. Because of the known potential and the ability of a mutagenic substance to induce cancer in animals, this finding raises serious questions concerning safety of iodine as a topical disinfectant. The halogens, including iodine, are capable of reacting with nucleic acids and their constituents and affect DNA. Although all of the aforementioned comments do not establish the fact that these drugs can cause cancer, this aspect of tumorigenesis cannot be ignored and requires further study. The argument that no ill-effects have been reported from long-term use is without merit and means little. Chloroform had been used as a flavorant in OTC oral health are products for years. It was not until recently that its potential for producing carcinoma was verified and its use in OTC products no longer allowed.

Topically applied antimicrobial agents may also activate the T-type lymphocytes in the tissues and cause delayed type of sensitivity. This results in allergic contact dermatitis on the skin if the drug is distributed to the skin by systemic transport. They may also act on the T-lymphocyte system in the mucous membranes and cause stomatitis and other local ulcerations of the mouth, throat, and gums. Antiseptics may also cause allergic reactions of Type I involving IgE such as anaphylaxis, rhinitis, angioedema, etc. (See part II. paragraph E. above—Adverse Reactions.) If absorbed, systemic allergic reactions may occur.

The relationship of plaque formation and production of caries has not been definitely established. Should there be a definite relationship between antimicrobial activity in plaque and development of caries and should an antiseptic be indicated for prophylaxis, it is the feeling of the Panel that preparations that can be applied locally to the teeth, such as pastes or powders, are indicated. The Panel considers the periodic flushing of the entire oral cavity, which is not involved in cariogenic activity, with an antiseptic for prophylactic purposes is a procedure of doubtful rationality and one that should be discouraged.

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*B. Categorization of Data*

1. *Category I conditions under which antimicrobial active ingredients for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

**Category I Active Ingredients**

None.

**Category I Labeling**

a. *Indication.* The Panel did not classify any antimicrobial active ingredient in Category I, but did place some ingredients in Category III. Because additional testing is necessary to determine the actual effect these ingredients have in the mouth and throat, the Panel did not place any indication in Category I. The Panel has proposed a Category III indication for oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

b. *Warnings*(1) *For all products containing oral health care antimicrobial active ingredients.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing oral health care antimicrobial active ingredients used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which antimicrobial active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral health care antimicrobial drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredients**

Boric acid
Boroglycerin
Camphor
Cresol
Ferric chloride
Meralein Sodium
Nitromersol
Potassium chlorate
Sodium dichromate
Tincture of myrrh

a. *Boric acid.* The panel concludes that boric acid is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boric acid ($H_3BO_3$) is also known as boracic acid or orthoboric acid. It occurs as a colorless or white powder or as scales or granules with a slightly bitter taste. It has a molecular weight of 61.844 and a melting point of 184° C.

One gram of boric acid dissolves in 18 mL of cold water or in 4 mL of boiling water. It also dissolves in 18 mL of cold alcohol, 6 mL of boiling alcohol, and in 4 mL of glycerol. Boric acid is used as a pharmaceutical necessity for buffering as well as for an active ingredient (Ref. 1). It is stable in air and incompatible with alkalis, carbonates, and hydroxides. Boric acid is prepared by the action of sulfuric acid on sodium borate.

A 2.5-percent solution of boric acid is said to be bacteriostatic, but not bactericidal. It is a mild topical astringent and drying agent with anti-inflammatory and antipruritic effects. In concentrations ordinarily used clinically, boric acid does not irritate or devitalize tissues (Ref. 2). It has been found that concentrations greater than 2 percent may inhibit phagocytosis, thereby negating a primary defense mechanism of the body against bacterial invasion (Ref. 3).

Elemental boron is an essential element for plant life, but this does not appear to be the case for animal life.

(1) *Safety.* The Panel concludes that boric acid is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Absorption of boric acid occurs readily from the mucous membranes of the mouth, throat, gastrointestinal tract, and from the lining of hollow viscera. It is also absorbed from the surface of the vagina, the lining of the conjunctival sac, from abraded or denuded skin, and from wounds (Ref. 4). The absorption of toxic doses may occur rapidly, yet toxic symptoms may be delayed for hours. Intact, healthy skin apparently acts as an effective barrier for boric acid (Refs. 5 and 6); however, there are differing opinions in the literature concerning this point (Refs. 7, 8, and 9). Seventy to 90 percent of an oral dose of boric acid is excreted in the urine unchanged. Only small amounts are found in the feces, saliva, and perspiration. Excretion of boric acid is not influenced by fluid intake but is significantly delayed by renal disease. About 50 percent of a dose is excreted within the first 12 hours, and the remainder is eliminated over a period of 5 to 7 days (Ref. 10). During chronic administration, elimination is slow. A plateau in urinary excretion usually is reached after 2 weeks (Refs. 5 and 6). Thus, there is a tendency for accumulation to occur with chronic use. There is a greater amount of boron in the brain when accumulation occurs, than at the site of treatment, especially wounds (Refs. 5 and 6). Large amounts are also found in the liver and the kidney. Kidney damage occurs when toxic doses are ingested.

The oral $LD_{50}$ for dogs is greater than 1,000 mg/kg. The subcutaneous $LD_{50}$ for guinea pigs is 1,200±80 mg/kg. In the mouse, the oral $LD_{50}$ is 3,450 mg/kg. In the rat, the oral $LD_{50}$ is 5,140 mg/kg.

The exact lethal dose of boric acid in humans is not known. Death has occurred from ingestion of less than 5 g in infants and from 5 to 20 g in adults. Amounts of this magnitude can be absorbed readily when boric acid solutions are used to irrigate closed cavities (Ref. 11). In a study of 100 cases of accidental poisoning, the overall fatality rate was 55 percent, but in infants under 1 year of age, 70 percent ended fatally (Ref. 12).

The symptoms of poisoning from boron derivatives are nausea, vomiting, diarrhea, and epigastric pain. Vomiting is often persistent and the vomitus and feces may contain blood. Hemorrhagic gastroenteritis may develop irrespective of the route of administration. Both the vomitus and stools have a blue-green color. Weakness, lethargy, headache, restlessness, irritability, tremors, and intermittent convulsions with subsequent depression of the central nervous system occur. Skin eruptions and kidney and liver damage have also been reported.

In 1962, 172 cases of boric acid intoxications with 89 deaths were compiled from the literature. In 53 cases, the drug had been used externally. Death occured in 23 of 30 children with diaper rashes (Ref. 13). The American Academy of Pediatrics has condemned this drug and recommended that its use be abandoned.

It is the consensus of the Panel that all OTC products containing boric acid and recommended for topical use on the mucous membranes of the mouth and throat likewise be condemned.

(2) *Effectiveness.* The Panel concludes that boric acid is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boric acid and its sodium salt have weak bacteriostatic and fungistatic activities. Neither the salt nor the acid is germicidal or fungicidal even in saturated aqueous solutions. A 2.5-percent aqueous solution will stop the growth of almost all forms of bacilli. They are not destroyed, however. The growth of the anthrax bacillus is inhibited, but is not halted when exposed to a 4-percent solution of boric acid. Furthermore, when removed from the boric acid solution anthrax bacilli once again begin to grow uninhibited (Ref. 14). Boric acid, therefore, is of

doubtful value as an antiseptic and is only suitable for bacteriostatic purposes. It has the advantage over other antimicrobial agents with bacteriostatic activity in that it induces very little irritation of wounds or delicate tissues such as the conjunctiva and mucous membranes of the eye, nose, mouth, throat, or even the gastrointestinal tract. Boric acid was, once upon a time, used as a preservative for foods, some medicines, and cosmetics. Its use for this purpose is now forbidden by law.

The mode of action of boric acid as a bacteriostatic agent is not known. Whether or not its effect is due to the hydrogen ion released from the acid is not known. Solutions of 0.3 percent inhibit putrefaction and decomposition, but do not inhibit the growth of pathogenic organisms.

The bacteriostatic effectiveness of boric acid varies with different types of bacterial cultures. It begins to manifest bacteriostatic activity at approximately a 1/20 saturated aqueous solution and does not appear to increase in activity after concentrations are 1/6 saturated.

Boric acid and sodium borate have no disinfectant properties. The chemically allied salt, borax ($Na_2B_4O_7$), is alkaline and also manifests bacteriostatic activity. Borax is less active than the acid, and it acts to some extent as a debriding agent due to its alkalinity.

(3) *Evaluation.* The Panel classifies boric acid, sodium borate, and borax as Category II from both the standpoint of safety and effectiveness as a topical antimicrobial agent in the mouth and throat. The reaons for this are because of their toxicity, since they are derived from boron, and because of their questionable bactericidal and disinfectant effects.

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b. *Boroglycerin glycerite.* The Panel concludes that boroglycerin glycerite is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boroglycerin glycerite is made by dissolving boroglycerin in glycerin. Boroglycerin is glycerin borate. It is also know as glycerite of boric acid, glyceritum boroglycerin, and glyceritum acidi borici. Boroglycerin when dry is a white, transparent, glassy, brittle, hygroscopic substance which forms a mass as it stands and absorbs water. It is soluble in hot water and, in solution, undergoes cleavage to glycerin and boric acid. Boroglycerin is not used as such, but instead, is converted to boroglycerin glycerite and used as an antimicrobial agent (Ref. 1). Boroglycerin glycerite is prepared by heating two parts of boric acid with three parts of glycerin, which is then dissolved in glycerin. Boroglycerin glycerite is a 50-percent solution of boroglycerin ($C_3H_3BO_3$) in glycerin (Ref. 2). Boroglycerin glycerite is a sweet, syrupy hygroscopic liquid. In aqueous solution, boroglycerin is more highly ionized than boric acid. As a consequence, its solutions are more irritating than those of boric acid. Boroglycerin glycerite was once, but is no longer, official in the "United States Pharmacopeia." Both boroglycerin glycerite and boroglycerin should be kept in tightly stoppered containers because they are hygroscopic.

(1) *Safety.* The Panel concludes that boroglycerin glycerite is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boroglycerin glycerite is not safe because it is a derivative of boric acid and its action is due to the release of boric acid when boroglycerin glycerite is applied to wounds, burns, and other, lesions and on the mucous membranes of the mouth and throat. No data are available on the acute and chronic toxicity of boroglycerin or boroglycerin glycerite. Inasmuch as boroglycerin and boroglycerin glycerite are derivatives of boric acid and release boric acid during clinical use, it is the consensus of the Panel that their toxicity is similar to that of boric acid. (See part IV. paragraph B.2.a. above—Boric acid.) Glycerin, their other component, is relatively innocuous.

(2) *Effectiveness.* The Panel concludes that boroglycerin glycerite is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boroglycerin glycerite contains 31 parts of boric acid and 96 parts glycerin. The anitimicrobial action of boroglycerin is due to the boric acid, which is slowly released when applied to burns. It is used externally, diluted with 10 parts of water. Since the active ingredient is boric acid, it can only be assumed that boroglycerin glycerite is not an effective antimicrobial agent. There are no controlled studies reported that establish it as an effective antimicrobial agent. Data on its effectiveness have not been supplied to the Panel in the submissions by manufacturers, and the Panel doubts that it is any more effective than boric acid. (See part IV. paragraph B.2.a. above—Boric acid.)

(3) *Evaluation.* The Panel concludes that boroglycerin glycerite be placed in Category II for both safety and effectiveness because it contains a boron derivative.

**References**

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c. *Camphor.* The Panel concludes that camphor is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The general characteristics of camphor have been described elsewhere in this document. (See part III. paragraph B.2.b. above—Camphor.)

(1) *Safety.* The Panel concludes that comphor is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The safety of camphor has been descried elsewhere in this document. (See part III. paragraph B.2.b.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that camphor is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Applied locally, camphor is alleged to be weakly antiseptic, but no controlled studies have been submitted to support this contention. Camphor is a ketone and, as is common with other ketones, lacks antiseptic activity. Furthermore, the Panel has not evaluated any ketone that is a safe and effective antiseptic. Camphor is a rubefacient when rubbed on the skin. When not applied vigorously, however, it may produce a feeling of coolness. This sense of coolness is also felt when camphor is applied to the mucous membranes. Camphor has a mild local anesthetic action, and its application to the mucous membranes in appropriate concentrations may be followed by numbness.

Camphor is absorbed through both the mucous membranes and from the skin. Camphor is also used for its local anesthetic and antipruritic effect to relieve itching of the skin. It has been used in conjunction with phenol for local application to treat fungal infections. It is believed that camphor retards the release and absorption of phenol from a mixture, but instances of ulceration from single applications of the mixture have been reported. (Ref. 1). Camphor is dispensed as camphor oil liniment, camphor in soap liniment, and spirits of camphor, which is a 10-percent solution by weight and volume, of camphor in alcohol. This mixture of camphor and alcohol is locally irritating when applied topically. Camphor water is a saturated solution of camphor in purified water. It is sometimes used for its supposed astringent effect.

(3) *Evaluation.* The evaluation of camphor has been described elsewhere in this document. (See part III. paragraph B.2.b.(3) above—Evaluation.)

**Reference**

(1) Hubler, W. R., "Ulceration of the Feet Following Single Application of Camphor-Phenol Mixture," *Journal of the American Medical Association,* 123:990, 1943

d. *Cresol.* The Panel concludes that cresol is not safe and that there are insufficient data to classify cresol as an effective antimicrobial active ingredient for topical use on the mucous membrances of the mouth and throat.

Chemically, cresol is phenol with a methyl group on either the ortho, meta, or para positions of the benzene ring. Thus, cresol can exist in three isomeric forms. The pure forms of each are available but generally the mixture of the three is used for general and medical purposes. The cresols are obtaind by the fractional distillation of coal tar or petroleum. The mixture is predomintely metacresol which is the most toxic of the three. When the term "cresol" is used, generally the mixture is meant. Cresol is also known as tricresol, methylphenol, or cresylic acid. Cresol may contain traces of phenol.

Cresol consists of a colorless, pinkish or yellowish to brownish liquid which is highly refractory. Not less than 90 percent by volume distills betwen 195 and 205° C. It darkens with age and on exposure to light, as does phenol (Ref. 1). One milliliter dissolves in approximately 50 mL water, usually producing a cloudy solution. It is miscible with alcohol, glycerin, ether, and other organic solvents (Ref. 2). Like other phenols, it is acidic in reaction in aqueous solutions and forms salts in soluble alkaline metal hydroxides. Cresol is also dissolved in camphor to form a complex, camphor metacresol. This complex is similar to the camphor-phenol complex and releases cresol when it comes in contact with moisture (Ref. 3).

(1) *Safety.* The Panel concludes that cresol is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Because cresol is closely allied to phenol both chemically and parmacologically, it behaves as does phenol. Fatal cases of cresol poisoning have followed the ingestion of the drug or its use as a douche. It is readily and rapidly absorbed from the skin and mucous membrances. Cresol is somewhat less toxic than phenol due to the presence of the methyl group on the benzene ring. The symptoms of cresol poisoning and the treatment are similar to those for phenol. (See part III. paragraph B.l.g. above—Phenol.) When applied locally to the skin, cresol causes a burning sensation and an erythema, followed by numbness. It acts in the same manner as phenol and destroys tissue, cauterizing the area of application. After oral ingestion, severe burning sensations in the mouth and upper abdomen are felt. Dysphagia, vomiting, and diarrhea are common. White spots are seen on the mucous membranes after ingestion, indicating that the cresol has coagulated the cellular protein. It behaves exactly as does phenol in this regard (Ref. 4). Unconsciousness and circulatory collapse follow. If the patient survives, jaundice, oliguria, and uremia may develop due to injury to the liver and kidneys. Orally 8 g or more have been fatal to man. Cresol is a general protoplasmic poison. Data on absorption from the mucous membrances of the mouth and throat were not available, but the Panel surmises that it behaves like other phenols and is absorbed and passes into the systemic circulation and, therefore, has all the drawbacks of phenol.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of cresol as an OTC antimicrobial active ingredient for tipical use on the mucous membrances of the mouth and throat.

Cresol is an antimicrobial agent that surpasses phenol in germicidal and antiseptic activity. The substitution of an alkyl (methyl) radical or other side chain on the aromatic nucleus of phenol enhances its antimicrobial activity. Cresol is about three times more active than phenol as a germicide against many bacteria. It is four times more active against *Salmonella typhi* than phenol. The ortho isomer is the most actively germicidal of the three. Since cresol is sparingly soluble in water, it is generally employed in the form of a 50-percent solution dispersed with soap (saponated cresol solutions), which forms a clear solution with purified water, but a cloudy one with tap water because a precipitation of lime soaps occurs. Cresol is used largely for sterilization and sanitization and has limited use clinically as an antiseptic. Cresol has been used for sterilization of instruments in a 3- to 5-percent solution of the saponated mixture. One percent of saponated solution has been used for application to wounds. A 2-percent solution of cresol is suitable as a handwash. Cresol is used to disinfect excreta of patients with contagious diseases. Cresol is sometimes employed in a concentration of 0.25 to 0.5 percent as a bacteriostatic agent in parenteral solutions. A 0.2-percent aqueous solution has been used as a vaginal

douche, but is not recommended because adverse effects have resulted (Ref. 5).

Dilute solutions of cresol possess a topical anesthetic effect similar to that of phenol. It is, however, not used for this purpose.

Cresol must not be confused with creosol or creosote. Creosote is a mixture of phenols obtained from wood tar. The active ingredient in creosote is creosol, which is a methoxy cresol.

(3) *Evaluation.* The Panel has classified cresol as Category II because it is a phenol derivative which is caustic when applied topically and toxic when absorbed systemically. It produces local damage to tissues even in dilute solutions. Other agents are safer.

**References**

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(5) OTC Volume 130006.

e. *Ferric chloride.* The Panel concludes that ferric chloride is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Ferric chloride ($FeCl_3$) occurs as hexagonal dark leaflets or plates. It is red by transmitted light and green by reflected light. Ferric chloride is very hygroscopic and melts and volatilizes at about 300° C. In air, it readily absorbs water to form the hexahydrate ($FeCl_3 \cdot 6H_2O$). Ferric chloride is readily soluble in water, alcohol, ether, and acetone. It has also been referred to as iron perchloride (Ref. 1).

The hexahydrate forms brownish-yellow or orange monoclinic crystals which are readily soluble in water, alcohol, acetone, and ether. Aqueous solutions are acid in reaction. The hexahydrate is described as an astringent and stypic (Ref. 1). Aqueous solutions of ferric chloride have been described in the "National Formulary." Each 100 mL of these solutions contained 37.2 to 42.7 g ferric chloride (Ref. 2). The solution was used as an astringent and styptic to arrest bleeding from cut surfaces and wounds. The tincture was also described in the "National Formulary." This was a yellowish-orange solution with an ethereal odor which is due to the formation of ethyl chloride and ethyl acetate by the action of the acid liberated from the iron chloride. It was also known as "iron perchloride tincture." The tincture consisted of 15 g ferric chloride in 100 mL of 58 to 64 percent ethyl alcohol. It was used orally but was highly irritating to the gastric mucosa.

Ferric chloride solutions and acid tinctures are incompatible with alcohols, iodides, tannin-containing solutions, and acadia mucilage.

(1) *Safety.* The Panel concludes that ferric chloride is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The oral $LD_{50}$ in rats for iron chloride hexahydrate is 900 mg/kg. In rabbits, the intravenous $LD_{50}$ is 7.2 mg/kg (Ref. 3).

No data were submitted to the Panel on acute and chronic toxicity studies in animals or on the teratogenicity and carcinogenicity of the compound. No data on acute or chronic toxicity in man were submitted. It is stated that the anhydrous form is an irritant (Ref. 1).

According to Gosselin et al. (Ref. 4), ferric chloride has a toxicity rating of 3 and the probable oral lethal dose in man is 0.5 to 5.0 g/kg. When given orally, both ferric and ferrous soluble compounds induce essentially the same type of toxic syndromes. The symptoms of poisoning due to derivatives of iron are severe gastritis or gastorenteritis with abdominal pain and prolonged vomiting beginning 10 to 60 minutes after ingestion. Vomitus may become bloody. Diarrhea is sometimes violent, and the feces are watery and later tarry. Dehydration becomes intense, and generalized itching may occur. Shock, pallor, cyanosis, coldness, rapid, weak, or imperceptible pulse, low blood pressure, and rapid and shallow respirations occur. Breathing is deep and rapid indicating the presence of a condition of metabolic acidosis. Drowsiness, hyporeflexia, dilated pupils, and coma may occur. Liver injury, consisting of hemorrhagic necrosis may occur, but it is usually reversible. Death from shock may occur within 4 to 5 hours. Sometimes, following apparent recovery, pneumonia with fever or secondary shock may develop and cause death 1 to 3 days later. Pyloric stenosis and mild hepatic cirrhosis may be encountered as sequelae among survivors, but recovery is usually complete without sequelae.

(2) *Effectiveness.* The Panel concludes that ferric chloride is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The tincture of iron chloride is an effective protein precipitant and was once used as a styptic. It also has been used as an astringent. The tincture has been mixed with equal parts of glycerin and water and applied to the throat by means of a swab to relieve pharyngitis. It has also been used as a gargle, but it is no longer recommended for this purpose because of its questionable effectiveness. In addition, the acidity of the solution is injurious to the teeth (Ref. 5). No data are available from controlled studies concerning the spectrum of its antimicrobial activity (Ref. 6). The antimicrobial effects tincture of iron chloride may manifest presumably are due to its protein-precipitating properties.

Ferric chloride preparations are not recommended for internal use.

(3) *Evaluation.* The Panel concludes that ferric chloride preparations are not safe for internal use. Furthermore, the Panel has no data on the antimicrobial effects of ferric chloride and concludes that preparations containing ferric chloride are not effective for topical use as antimicrobial active ingredients on the mucous membranes of the mouth or throat.

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(3) Sector, W. S., editor, "Handbook of Toxicology: Volume I," W. B. Saunders Co., Philadelphia, pp. 140–141, 1956.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th E., Williams and Wilkins, Baltimore, section II, p. 97, and section III, p. 156, 1976.

(5) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co, Philadelphia, p. 1248, 1957.

(6) OTC Volume 130052.

f. *Maralein sodium.* The Panel concludes that meralein sodium (merodicein) is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Meralein soidum, better known as merodicein, is an organic mecurial antiseptic. Meralein sodium is (3'-6'-Dihydroxy-2', 7'-diiodospiro [3H-2, 1-benzoxanthiole-3, 9'-[9H]xanthen]-4-yl)-hydroxymercury 5,5-dioxide monsoidum salt; o-[6-hydroxy-5-)hydroxymercuri)-2, 7-diiodo-3-oxo-3H-xanthen-9-yl]-benzenesulfonic acid sodium salt; 2, 7-diido-4-hydroxymercuriresorcinsulfonphthalein monosodium salt (Ref. 1). Maralein

sodium is used as a topical antiseptic. It is supplied as a 1:5,000 aqueous solution for use in the mouth (Ref. 2). Meralein sodium consists of green scales that turn dark red. It is soluble in water. Aqueous solutions are slightly fluorescent.

(1) *Safety.* The Panel concludes that meralein sodium is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Gosselin et al. (Ref. 2) rate the toxicity of meralein sodium as 4 (very toxic). The probable lethal dose is 50 to 500 mg/kg. Gosselin et al. describe it as "A water-soluble germicide containing about 23 percent organically bound mercury." The minimal lethal dose parenterally in laboratory animals is 10 mg/kg. It is poorly absorbed from the gastrointestinal tract. Doses of 200 mg/kg have a laxative effect.

In an extensive study of the pharmacology and toxicology of meralein sodium, Macht and Cook (Ref. 3) showed that systemic poisioning was due to acute renal failure and found little effect on other organ systems. Gosselin et al. (Ref. 2) also showed that systemic poisoning leads to acute renal failure. When injected intravenously in a concentration of from 0.1 percent to 2.0 percent meralein sodium was carried by the circulation to the various organs where it conferred a pink color to the stomach, intestines, and other viscera (Ref. 2). Very little of the compound was deposited in the skin. Most of the meralein sodium was excreted via the intestinal tract, but small quantities were found in the urine and trace amounts in the bile. The saliva, even after pilocarpine was administered to promote the flow of saliva, contained no trace of the drug (Ref. 2).

(2) *Effectiveness.* The Panel concludes that meralein sodium is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Like many other mercurial antiseptics, meralein sodium is primarily bacteriostatic with bactericidal activity occurring slowly over a period of many hours. Bacteriostasis is readily nullified by the presence of many organic compounds, particularly those containing sulfhydryl radicals, such as thioglycollate, cysteine, and dimercaprol, and by glutathione, serum, and plasma (Ref. 4). This reversible bacteriostasis was clearly demonstrated by Engley (Ref. 5), who showed that virulent streptococci exposed to 0.2 percent meralein sodium for 10 minutes killed 10 out of 10 mice injected intraperitoneally. When the cells from the meralein sodium-treated cultures were transferred to dextrose broth, no growth occurred, but the addition of 0.1 thioglycollate or 10 percent serum to the broth enabled growth to occur in vitro just as it had in vivo.

One study indicates that the growth of *Staphylococcus aureus, Streptococcus pyogenes,* and *Pseudomonas aeruginosa* is merely inhibited when exposed to meralein sodium in a 1:5,000 concentration for 15 minutes, but that these bacteria are killed after 24 hours of exposure (Ref. 6). However, this is not of any clinical significance because it is unlikely that meralein sodium would remain in the mouth for more than 15 minutes and certainly not as long as 24 hours.

(3) *Evaluation.* The Panel concludes that the bacteriostatic effects of meralein sodium are transitory and insignificant. The bactericidal effects, likewise, are not significance since they occur slowly. Data on absorption from the mucous membranes are not supplied. Since the compound contains 23 percent mercury, it is not surprising that renal damage has been reported following its use. The Panel considers the compound toxic and not safe or effective for topical use in the mouth and throat.

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(6) OTC Volume 130075.

g. *Nitromersol.* The Panel concludes that nitromersol is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Nitromersol is identified with the mercurial organic compounds that are used for antimicrobial purposes. Nitromersol is the anhydride of 4-nitro-3-hydroxymercuriocresol. It is prepared from orthotoluidine through a succession of steps of nitration, diazotization, and interaction with mercuric acetate resulting in a crystalline powder.

Nitromersol is considered an organic mercurial. The organic mecurials are compounds in which mercury is present in complex organic combination. As a group they are more bacteriostatic, less irritating, and less toxic than the inorganic mercurial salts. Nitromersol is composed of brownish to yellow granules or a brownish-yellow powder. It is odorless, insoluble in water, almost insoluble in alcohol and ether, but soluble in solutions of alkalis (Ref. 1).

(1) *Safety.* The Panel concludes that nitromersol is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Mercuric compounds can be absorbed and can be toxic to the renal tubules of the kidney. This action is less pronounced by organic mercurial compounds than by the inorganic mercurial compounds. Nitromersol has a slight protein-precipitating action. Like other mercurials, it has a tendency to sensitize the skin.

(2) *Effectiveness.* The Panel concludes that nitromersol is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The mechanism of action of mercurial compounds is not known exactly. It is believed that the mercuric ion inhibits the activity of enzymes containing sulfhydryl groups (SH) by combining reversibly with these groups. The inhibition of these enzymes by mercury, therefore, is reversible. When the metal is removed from the enzyme, the activity is restored. Bacteria and certain viruses inactivated by mercury compounds can be reactivated by removing the mercury with the use of thiols. Bacterial spores exposed to mercurials for many months resume multiplication when the inhibitor is removed. In the body fluids there are many sulfhydryl compounds such as glutathione, cysteine, and proteins which are capable of combining with mercury. Organisms inhibited by mercury therefore, can become reactivated when they are introduced into the body.

The mercurial antiseptics inhibit the sulfhydryl-containing enzymes of tissue cells of the host as well as those of the bacteria. Test objects such as embryonic tissue and other cells are readily injured by organic mercurial compounds. The therapeutic index of organic mercurial compounds is low. They are not considered ideal antiseptics and germicides.

The organic mercurial compounds are employed as substitutes for the more highly ionized mercury salts because they are less irritating and can be applied directly to the tissues. They have been widely used in

concentrations ranging from 1:100,000 to 1:1,000 to disinfect instruments and as antiseptics on cutaneous and mucosal surfaces. However, they are not efficient for disinfecting instruments, as is commonly believed. The organic mercurial compounds are primarily bacteriostatic and are relatively ineffective in killing spores. The organic mercurial antiseptics are available as various types of proprietary solutions, tinctures, jellies, ointments, and suppositories (Ref. 2).

Although several investigators reported sterilization of the skin with the use of an application of a 1:5,000 solution of nitromersol which is a first-aid solution, White and Hill (Ref. 3) found that this compound could not be relied upon to produce sterility when applied to the skin for 5 minutes. A 1:200 alcohol acetone solution is highly effective as an antiseptic. The solution called nitromersol tincture is used for preoperative preparation of the skin. Nitromersol is available in a 1:500 solution in water. Since nitromersol is not readily soluble in water, a mixture of sodium hydroxide and sodium carbonate are used to convert the nitromersol to a soluble compound. A 1:200 tincture in 10 percent acetone, 52.5 percent alcohol by volume, and distilled water, is available.

No data were submitted to the Panel establishing the effectiveness of nitromersol as an antimicrobial agent for the relief of sore throat and sore mouth.

(3) *Evaluation.* The Panel concludes that nitromersol is not safe because of its toxicity and sensitization potential. There are no data from controlled studies showing that nitromersol causes relief of symptoms due to sore throat or sore mouth resulting from antimicrobial activity.

**References**

(1) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1096, 1975.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott, Philadelphia, p. 789, 1973.

(3) White, E. C., and J. H. Hill, "Inefficiency of Metaphen as a Skin Disinfectant," *Journal of the American Medical Association,* 95:27–28, 1930.

h. *Potassium chlorate.* The Panel concludes that potassium chlorate is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium chlorate occurs as colorless, lustrous crystals, as white granules, or as a white powder. It is odorless and has a cooling effect and a saline taste. One part potassium chlorate is soluble in 16.5 parts water. It is soluble in glycerin and slightly soluble in alcohol. Potassium cholorate should not come into contact with readily oxidizable substances because it forms explosive mixtures. Potassium chlorate explodes when mixed with sulfuric acid. It ignites and explodes if triturated with organic substances, such as sulfur, phosphorus, sulfite, hypophosphite salts, and other oxidizable substances. Potassium chlorate is incompatible with iodides and tartaric acid (Ref. 1).

(1) *Safety.* The Panel concludes that potassium chlorate is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium chlorate is not safe for internal use. Potassium chlorate poisoning was common when the drug enjoyed widespread use therapeutically. The poisoning resulted from overdose or from variations in susceptibilities and tolerance among different individuals. Ten grams are toxic; 15 to 30 g have been fatal. The mortality rate is about 70 percent when lethal doses are ingested. The symptoms may appear shortly after ingestion or may be delayed for 5 to 6 hours. Death has occurred as early as 6 hours and as late as 7 days after ingestion. Potassium chlorate is irritating to the gastrointestinal tract and the kidneys. Symptoms include nausea, vomiting, gastroenteritis, anemia, and hematuria. Gosselin and associates (Ref. 2) rate potassium chlorate as having a toxicity of 4 (very toxic). The chlorate ion is not metabolized readily and persists in the body for a long time. It may convert an indefinite amount of hemoglobin to methemoglobin. Asphyxia may result from the methemoglobinemia. The drug also causes hemolysis. The hemolyzed cells may produce emboli, and the released hemoglobin causes hematuria. It may also cause nephritis.

Chlorates are excreted mainly by the kidney into urine. About 90 percent of a dose is eliminated unchanged. The urinary excretion of a dose begin promptly and is complete within 24 to 48 hours. Chlorates are also partly excreted by the salivary glands into the mouth. When chlorates were first introduced into therapeutics, they were considered to be innocuous and safe. This has not proved to be the case as time has passed.

(2) *Effectiveness.* The Panel concludes that potassium chlorate is not effective as an antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium chlorate solutions, in concentrations ranging from 2 to 4 percent, have been used as mouthwashes and gargles for infections of the mouth and throat, even though they are potentially toxic and of questionable value (Ref. 3). The saturated solution has been used as a mouthwash to treat stomatitis, particularly when ulcerative lesions have been present. Potassium chlorate was introduced because it was believed that it would act as an oxidizing agent and exert antiseptic action by releasing oxygen. This does not appear to be its mode of action. It is eliminated largely unchanged and is not altered in the body.

Potassium chlorate is of doubtful effectiveness since there are no data from controlled studies to support the claim that it relieves symptoms of sore throat or sore mouth or both when used as an antimicrobial agent. It has been used in lozenge form. This imparts a "clean" saline taste of potassium chlorate to the mouth, which supplants the normally existing "unflavored taste." Potassium chlorate also is used in tablet form. The tablets consist of 0.25 g of the salt and are placed on or beneath the tongue two to five times daily where they slowly dissolve and exert their therapeutic affect. After using the tablets for several days, the saline taste persists due to the salt that is excreted into the mouth from the salivary and other exocrine glands (Ref. 4).

Chlorates do not manifest antimicrobial activity in cultures. How it came to be adopted as an antimicrobial agent has puzzled physicians.

Potassium chlorate has been combined with ferric chloride and balsam of tolu for use as a demulcent, and with glycerite and boroglycerin (Ref. 5).

(3) *Evaluation.* It is the consensus of the Panel that potassium chlorate is neither safe nor effective as an OTC active antimicrobial agent for topical use in the mouth and throat and that it be placed in Category II.

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 990, 1976.

(2) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 76, 1976.

(3) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, p. 891, 1977.

(4) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, pp. 794–795, 1947.

(5) OTC Volume 130052.

i. *Sodium dichromate.* The Panel concludes that sodium dichromate (also bichromate) is not safe and that there are insufficient data to classify its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Sodium dichromate is a derivative of chromium. Elemental chromium is used in medicine in the form of sodium or potassium dichromate. Sodium chromate is the sodium salt of chromic acid. The empiric formula for sodium chromate is $Na_2CrO_4 \cdot 4H_2O$. Sodium chromate loses its water of hydration to form an anhydrous salt. It also forms a crystalline hydrate with 10 molecules of water. The anhydrous form is a yellow powder. The hydrated form is soluble, about 1 part in 1 part of water. The aqueous solution is alkaline. Sodium chromate is also slightly soluble in alcohol. It is used to prevent rusting of iron.

The potassium salt ($K_2CrO_4$) has similar properties as the sodium salt. Sodium dichromate ($Na_2Cr_2O_7$) and potassium dichromate ($K_2Cr_2O_7$) are prepared by reacting sodium or potassium chromate with sulfuric acid (Refs. 1 and 2). Sodium chromate forms a dihydrate which consists of copper-colored, bright orange, or yellowish crystals. Its solutions are acidic. The pH of a 1-percent solution is 4, and the pH of a 10-percent solution is 3.5. The chromates are combined with sulfuric acid for cleaning glassware in laboratories (Ref. 1).

(1) *Safety.* The Panel concludes that sodium dichromate is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Chromium derivatives are used in medicine in the form of chromic acid or in the form of either the sodium or potassium bichromates. They are also used in the disodium and dipotassium forms. Derivatives of chromium are active oxidizing agents. In addition, they are poisons when ingested since they form chromous oxide, CrO, which is the anhydride of chromic acid.

Gosselin et al. (Ref. 3) give sodium dichromate a toxicity rating of 4 to 5 with a mean lethal dose probably of about 10 g. It is highly corrosive to skin and mucous membranes. If ingested, violent gastroenteritis, peripheral vascular collapse, vertigo, muscle cramps, coma, hemorrhagic diathesis, fever, liver damage, and acute renal failure occur. Methemoglobinemia occurs probably due to sodium dichromate's oxidizing properties. Sodium dichromate also causes intravascular hemolysis, as is the case with chlorate salts. When dichromates are ingested orally they are reduced to chromous oxide and partly deposited as such in various organs. The remainder is excreted in the urine. Chronic nephritis is produced experimentally by intravenous injection of chromates. The toxic effects of chromium derivatives are not only due to the fact that the resulting oxide is a poison when ingested, but also because they act sumultaneously as oxidizing agents while they are undergoing the chemical changes to the oxide in the body (Ref. 4). Derivatives of chromium used in various manufacturing processes are considered to be industrial hazards since they are poisons. Extreme precautions are taken to avoid their ingestion, inhalation of powders of the salts, or cutaneous absorption when they are used for industrial purposes (Ref. 2).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of sodium dichromate as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Sodium dichromate and other derivatives of chromium have been used as antimicrobial agents because of their oxidizing effects. They have no use as therapeutic agents because of their extreme toxicity. They were formerly used as astringents for the treatment of excessive sweating of the skin and as caustic agents to remove cutaneous lesions, neoplasms, etc. They were also used internally to treat gastric ulcers. Aqueous solutions of 5 percent sodium dichromate have been used on the skin without irritation; however, 10 percent solutions are caustic. Two to 3 percent aqueous solutions have been used as astringents and antimicrobial agents (Ref. 5). The pharmacologic actions of the sodium derivative are similar to those of the potassium derivative (Refs. 2 and 4).

(3) *Evaluation.* The Panel concludes that sodium dichromate is not safe for topical use on the mucous membranes of the mouth and throat because it is absorbed, and the systemic toxicity that results is characterized by nephritis and other organic syndromes.

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1112, 1976.

(2) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 148, 1947.

(3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 76, 1976.

(4) Sollmann, T., " A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, p. 937, 1948.

(5) OTC Volume 130041.

j. *Tincture of myrrh.* The Panel concludes that tincture of myrrh is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Myrrh belongs to the class of substances known as balsams or aromatic resins. Myrrh is categorized as an oleoresin. The oleoresins, in general, are oily substances containing largely benzoic and cinnamic acids and other constituents. They are considered to be mildly irritant and to stimulate the repair of tissues because of the substances contained in their oily components (Ref. 1). The resins furnish local protection and allegedly allay inflammation. Balsams and oleoresins are applied in cases of chronic inflammation of the mucous membranes and of the skin to promote healing of ulcers and wounds (Ref. 2).

Myrrh, also known as myrrha, is a gum resin obtained from camphora species (Ref. 3). It was used by the ancients as incense in religious ceremonies and by the Egyptians for embalming in combination with spices and other substances. Myrrh was formerly listed in the "United States Pharmecopeia." The botanical source of myrrh is *Commiphora molmol.* It is also obtained from Commiphora abyssinica and other species of camphora. The name "myrrh" is possibly derived from the Arabic and Hebrew word "mur" meaning bitter, The drug was also called "mulmul" and "ogo" by the natives of Somaliland and "herrabol" by the Indian traders. Myrrh is collected in Somaliland and Arabia by making incisions into the bark of the stems of trees. A gum-oleoresin film forms and reservoirs of the fluid collect beneath this film. These are punctured, and the myrrh is allowed to exude. The myrrh then hardens and is scraped off the bark. Most of the drug used in the United States is gathered from Somaliland and Arabia. In 1952, 19,040 pounds of myrrh were imported from British Somaliland.

Myrrh yields not less than 30 percent of alcohol-soluble extractives and not more than 5 percent of acid-insoluble ash. It contains from 3 to 8 percent of an oxygenated volatile oil, a bitter principle, about 50 to 60 percent of gum, and 25 to 40 percent of resin. The resin contains three isomeric forms of commiphoric acid, an ester of commiphorinic acid, and two isometric

forms of myrrolic acid. The volatile oil, which has been called myrrhol or myrrhenol, contains eugenol, meta-cresol, cuminaldehyde, cinnamaldehyde, pinene, dipentene, a sesquiterpene, and esters of formic, acetic, and myrrholic acids. The gum, with properties similar to arabin and acacia, yields pentosans, galactans, xylans, and arabans upon hydrolysis. The gum also contains an oxidizing enzyme (Refs. 4, 5, and 6). Myrrh has been used both in its natural form and as a tincture. The preparation reviewed by this Panel is the tincture.

(1) *Safety.* The Panel concludes that tincture of myrrh is not safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

The ancient Greek physicians used myrrh locally as well as internally. Since it is an oleoresin, it has the properties of other oleoresins in being a mild irritant (Ref. 7). Because of these irritant properties, myrrh has been used as a component of laxative preparations. It has also been used in the form of the tincture which contains an alcohol-soluble extract of 20 percent of the drug. Internally, myrrh was once used as a carminative (Ref. 2). Myrrh and tincture of myrrh were official in "United States Pharmacopeia, XIII." They were not admitted to the "United States Pharmacopeia, XIV." They were admitted to the "National Formulary IX." They maintained official status until 1965 when both were dropped and not admitted to either compendium.

Animal toxicity studies, from which the Panel could make judgment, were not available.

(2) *Effectiveness.* The Panel concludes that tincture of myrrh is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The comments concerning tincture of myrrh's therapeutic effectiveness are merely anecdotal, and there are no controlled studies to substantiate that it is an effective active ingredient. Tincture of myrrh has been applied loclly to "stimulate" spongy gums, to treat aphthous stomatitis, and ulcerations of the throat (Ref. 6). In its diluted form, tincture of myrrh has been employed in mouth rinses, for treating stomatitis, and in other lesions of the oral cavity (Ref. 2). The dosage range of myrrh is 0.3 to 1.2 g. The dosage range of tincture of myrrh is 1 to 2 mL. It has been used as a component of aloes and myrrh pills and compound pills of rhubarb (Ref. 8). Both OTC preparations currently on the market contain myrrh as a component of a combination product of several ingredients.

The Panel concludes that, since myrrh is a mixture of many substances and that since it has fallen into disuse in general medical practice, it has no place in modern therapeutics. Obviously, myrrh has been supplanted by other medicines whose pharmacologic action has been established.

(3) *Evaluation.* The Panel concludes that myrrh is a mixture of many substances, the active principle of which has not been identified. There is a paucity of data on the pharmacologic activity and safety of myrrh, and it cannot be adequately evaluated. Myrrh has fallen into disuse, and the Panel concludes that tincture of myrrh should be placed in Category II.

**References**

(1) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, p. 49, 1965.

(2) Sollman, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, p. 147, 1948.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 822, 1976.

(4) Lyman, R. A., "Textbook of Pharmaceutical Compounding and Dispensing," 2d Ed., J. B. Lippincott, Philadelphia, p. 283, 1955.

(5) Darlington, R. C., "Topical Oral Antiseptics, Mouthwashes and Throat Remedies," *in* "Handbook of Non-Prescription Drugs," 4th Ed., edited by G. B. Griffenhagen and L. L. Hawkins, American Pharmaceutical Association, Washington, pp. 123–134, 1973.

(6) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott, Philadelphia, pp. 875–877, 1955.

(7) Thienes, C. H., and T. J. Haley, "Clincial Toxicology," 4th Ed., Lea and Febiger, Philadelphia, pp. 61–68, 1964.

(8) "The National Formulary," 6th Ed., American Pharmaceutical Association, Washington, pp. 396 and 399–400, 1935.

**Category II Labeling**

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use, or for description of product attributes for products containing antimicrobial agent active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Healing aid."

(2) "Relieves dryness."

(3) "For relief of pain and discomfort due to minor sore throat."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "For fast temporary relief of minor throat and mouth soreness."

(2) "Fast healing aid,"

(3) "Kills germs in minutes."

(4) "Kills germs by the millions on contact."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Multiaction germ killer."

(2) "Kills germs by the millions on contact."

(3) "General antiseptic application as an aid to wound healing."

(4) "Soothing cleansing antiseptic for mouth and throat."

(5) Adding such terms as "plus" etc.

d. *Statements or phrases that are vague in their meaning and that cannot be readily understood or are misleading.* (1) "Healing and for minor oral inflammations."

(2) "First aid for throat irritations."

e. *Statements or phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion the diagnosis of which must be made by a physician.* (1) "As an aid to professional care of minor inflammation of the mouth and throat."

(2) "Healing aid for minor oral inflammations."

(3) "For temporary relief of minor sore throat due to common cold."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom or disease state when proof that this occurs is lacking.* (1) "Prevents infection" (of the mouth and throat).

(2) "Helps provide breath protection."

(3) "As an adjunct for prophylaxis of Vincent's infection."

(4) "Healing and deodorizing solution."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "Inhibits odor forming bacteria."

(2) "Deodorizing mouth wash and gargle."
(3) "Oral antiseptic cleanser."
(4) "For oral hygiene."
(5) "For general oral hygiene, bad breath."
(6) "Management of mouth odors, bad breath,"
(7) "An aid to daily care of the mouth,"
(8) "Helps provide soothing temporary relief of dryness and minor irritations of the mouth."
(9) "For causing the mouth to feel clean."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic effect or class of a drug or type of formulation containing the ingredient(s) instead of designating the symptoms which the product is intended to relieve.* (1) "Antiseptic, oral antiseptic."
(2) "Antimicrobial."
(3) "Antiseptic drops."
(4) "An effective antiseptic when undiluted."

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

**Category III Active Ingredients**

Benzalkonium chloride
Benzethonium chloride
Benzoic acid
Carbamide peroxide in anhydrous glycerin
Cetalkonium chloride
Cetylpyridinium chloride
Clorophyll
Dequalinium chloride
Domiphen bromide
Ethyl alcohol
Eucalyptol
Gentian violet
Hydrogen peroxide
Iodine
Menthol
Methyl salicylate
Oxyquinoline sulfate (8-hydroxyquinoline)
Phenol
Phenolate sodium
Povidone-iodine
Secondary amyltricresols
Sodium caprylate
Thymol
Thymol iodide
Tolu balsam

a. *Benzalkonium chloride.* The Panel concludes that benzalkonium chloride is safe, but that there are insufficient data to classify its effectiveness as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzalkonium chloride is a mixture of alkyldimethylbenzylammonium chlorides with the empiric formula $[C_6H_5CH_2N(CH_3)_2R]$ Cl. R represents alkyl groups of varying lengths beginning with n-$C_8H_{17}$ to n-$C_{18}H_{37}$. The mixture is so composed that the average molecular weight of the final product is 360 daltons. It is emphasized that benzalkonium is not a single entity compound, but a mixture of very closely allied derivatives (Ref. 1).

Domagk, in 1935, called attention to the antiseptic and detergent properties of certain quaternary ammonium compounds and noted in particular that benzalkonium chloride was most effective (Ref. 2).

Benzalkonium chloride possesses the structural requirements for a quaternary ammonium compound having high germicidal activity, namely, the presence of a long alkyl hydrocarbon chain, one short aromatic-substituted alkyl group (benzyl), and two shorter alkyl groups (methyl). (See part IV. paragraph A.8.a above—The quaternary ammonium compounds.) The long alkyl hydrocarbon chain is obtained from the fatty acids of coconut oil; because the composition of coconut oil is reasonably constant, a uniform composition of the product is assured.

Benzalkonium chloride is usually available as a white to yellowish-white powder, but it may exist as a thick gel or as dried lumps of gelatinous pieces. It is very soluble in both water and alcohol. Aqueous solutions foam copiously when agitated.

Benzalkonium chloride is a cationic detergent, i.e., one whose antiseptic and detergent properties reside in the cation and as such is incompatible with any anionic detergent, such as soap, in which the detergent effect resides in the anion. Soap should be completely removed from tissues to which benzalkonium chloride solution is to be applied (Ref.3).

(1) *Safety.* The Panel concludes that benzalkonium chloride is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Effective concentrations of benzalkonium chloride are relatively nonirritating to the skin. They are said to have an emollient action. A 1:1,000 solution was given orally to guinea pigs as their only source of fluid for months without apparent harmful effects. Daily intraperitoneal injections of as much as 6 mL of the 1:1,000 solution for several months also showed no apparent reaction. Single doses of 1.2 mL/kg of body weight of a 10-percent solution produced little or no effect in rabbits when injected subcutaneously or intraperitoneally. When the dose was increased to 1.5 mL/kg, death occurred within 24 hours due to local destruction of tissue rather than systemic toxicity.

In reporting the death of a woman following artificial abortion with benzalkonium chloride, Arnold and Krefft (Ref. 4) stated that in animals the substance is extremely toxic following intraperitoneal or intravenous injection. It produced, according to these investigators, a curare-like effect with paralysis of neuromuscular junctions of all striated muscles, which was similar to the effect observed in the woman. Extreme caution is advised by Arnold and Krefft in using benzalkonium chloride for washing body cavities, especially if the solution is to be kept in place for a long time. These manifestations of toxicity are consistent with the pharmacologic behavior of many quaternary nitrogenous compounds. They manifest ganglionic blocking effects and a curare-like action.

There are little data of any significance obtained from controlled studies on the absorption of benzalkonium chloride from the mucous membranes. Quaternary nitrogenous compounds are highly ionized and, therefore, do not penetrate lipid barriers of the cell membrane since they are not lipophilic. They are not readily metabolized by the microsomal reticulum of the liver and are excreted almost entirely unchanged through the kidney. The Panel cautions, however, that the presence of a lipophilic group could modify absorption and possibly enhance it.

The Panel finds no data from controlled studies on the cumulative effects resulting from absorption from the mucous membranes of benzalkonium chloride when used on a day-to-day basis in mouthwashes or rinses for years. There are no data on the tumorigenic, mutagenic, or teratogenic potential of the agent when used under similar circumstances or during pregnancy.

The human fatal dose of quaternary nitrogenous cationic agents has not been established; it is believed to be between 1 and 3 g. Concentrated solutions are primary skin irritants, but percutaneous absorption is not considered to be significant. Although these agents can be haptenogenic and cause systemic and local allergic responses, the incidence of sensitization is low. Benzalkonium chloride is less injurious to human leukocytes than are the mercurial antiseptics (Ref. 5).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of benzalkonium chloride

as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzalkonium chloride is a powerful and rapidly acting germicide for many pathogenic nonsporulating bacteria and fungi. Solutions of the substance have a low surface tension (37.4 dyn/cm for a 1:1,000 solution at 25.3° C) and possess detergent, keratolytic, and emulsifying properties. All of these qualities favor wetting and penetration into surfaces to which solutions of benzalkonium chloride are applied. In vitro tests have demonstrated that *Streptococcus haemolyticus* is killed within 10 minutes (but not in 5 minutes) by a 1:40,000 solution at 20° C, and by a 1:95,000 solution at 37° C; for *Staphylococcus aureus* the corresponding letal dilutions are 1:20,000 and 1:35,000; for *Eberthella typhosa* they are 1:20,000 and 1:70,000; and for *Escherichia coli*, 1:12,000 and 1:40,000. In the presence of serum the effective concentrations were approximately 10 times greater (Refs. 6 through 9).

On the skin, under the usual conditions of use, the disinfectant action of benzalkonium chloride is not as great as has been generally supposed, principally because residual soap on the skin inactivates the detergent (Ref. 10). (See part IV. paragraph A.8. above—Quaternary nitrogenous cationic antimicrobial agents.) Thorough rinsing to the area to which benzalkonium chloride is to be applied, with water, will materially enhance its effectiveness. Price (Ref. 10) has demonstrated that the "tincture" of benzalkonium chloride, in which the solvent is composed of 50 percent ethyl alcohol, 10 percent acetone, and 40 percent water, is not only a more effective skin disinfectant than an aqueous solution of equal concentration, but also is less affected by soap than is the aqueous solution. The strongest disinfectant action, according to Price (Ref. 10), is produced by a 1-percent iodine solution in 70 percent alcohol; the next strongest is 70 percent alcohol; the next strongest is 70 percent (by weight) alcohol by itself; third is the tincture of benzalkonium chloride.

Miller and associates (Ref. 11) reported that certain cationic antiseptics of the type of benzalkonium chloride deposit an invisible film on the skin which is difficult to remove. This film may be sterile on the outside, but underneath it the skin may hold viable bacteria; it is readily removed by alcohol or by application of an anionic detergent, such as soap.

Adsorption of benzalkonium chloride by cotton guaze sponges placed in a solution of the compound, thereby reducing the germicidal effectiveness of the solution, may have been responsible for the viability of an organism isolated from a solution that caused infection when used for skin disinfection in a hospital (Ref. 12).

Aqueous or alcohol-acetone-water solutions of benzalkonium chloride may be employed on the skin to reduce the microbial population. Where the skin has been washed with soap and water, careful rinsing with water, then with 70 percent alcohol, is to be followed by application of the "tincture" of benzalkonium chloride. Aqueous solutions of benzalkonium chloride are employed on areas where soap is not ordinarily used or where alcohol would produce irritation.

Concentrations of benzalkonium chloride recommended for topical uses are as follows: preoperative disinfection of skin, 1:750 tincture or solution; minor wounds and lacerations, 1:750 tincture; deep infected wounds, 1:20,000 to 1:3,000; denuded skin and mucous membranes, 1:10,000 to 1:5,000; vaginal douche and irrigation, 1:5,000 to 1:2,000; bladder and urethral irrigation, 1:20,000 to 1:5,000; bladder retention lavage, 1:40,000 to 1:20,000 eye irrigation, 1:10,000 to 1:5,000; ear and antrum irrigation, 1:10,000 to 1:1,000; preservation of ophthalmic solutions, 1:7,500 to 1:5,000; storage of catheters and other adsorbent materials, 1:500; storage of thermometers, and metallic instruments, 1:750 (aqueous); general hospital disinfection, 1:25,000.

Benzalkonium chloride, in 1:5,000 concentration, was found by Lawrence (Ref. 13) to be the most effective of several agents evaluated for antimicrobial activity in ophthalmic solutions; at this concentration destruction of test organisms was achieved in 30 minutes.

Benzalkonium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel believes that benzalkonium chloride is of limited clinical usefulness as a topical antimicrobial agent for the temporary relief of occasional symptoms of sore mouth or throat because its antimicrobial spectrum is limited, especially by the uncertainty imposed by environmental factors such as the presence of proteins, neutralizing anions, and organic materials in the mouth. Furthermore, the evidence is overwhelming that the topical application of antimicrobial agents to infected and inflamed areas is of doubtful therapeutic value, is not necessarily curative, may not ameliorate a disease process, and may even aggravate an inflammatory state. Certain antimicrobial agents are of value for select infections for which the agent is specifically microbicidal. Such specific conditions can only be diagnosed by a physician or dentist and are not amenable to self-diagnosis or treatment by a consumer, such as would be appropriate for using OTC products.

The Panel does not recommend mouthwashes, rinses, sprays, or lozenges containing benzalkonium chloride as an antimicrobial agent for use as deodorants, cleansing, prophylaxis, or for oral health care on a daily basis or for protracted periods of time, particularly in situations that are devoid of symptoms. (See part IV. paragraph A.2. above—Antimicrobial agents for use in the oral cavity.)

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of benzalkonium chloride as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.01- to 0.02-percent concentration of benzalkonium chloride in the form of a rinse, mouthwash, gargle, spray, or by swabbing digitally or using a nonadsorbent applicator, not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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b. *Benzethonium chloride.* The Panel concludes that that there are insufficient data available to permit final classification of the safety and effectiveness of benzethonium chloride as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzethonium is identified with the group of surface active agents that possess antimicrobial activity belonging to the family of cations derived from pentavalent nitrogen. Four of the five bonds are covalent, and one is ionic. Benzethonium is a base derived by substituting the four hydrogen atoms of the ammonium ion with organic radicals. When dissolved in water, a base forms that is ionized into a quaternary ammonium ion and a hydroxyl ion. The base forms salts with organic and mneral acids, usually hydrochloric, in the same manner as does ammonium hydroxide. Benzethonium chloride is benzyldimethyl[2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxyl]ethyl]ammonium chloride and contains, on a dry basis, not less than 97 percent of $C_{27}H_{42}ClNO_2$. In an aqueous solution it ionizes and yields a substituted ammonium cation and a chloride ion. The biologically active ion is the substituted ammonium cation. It is similar in chemical structure to the other quaternary nitrogenous bases that possess antimicrobial activity. One of the substituents on the nitrogen atom is a high molecular weight aliphatic chain that confers lipophilic properties to the compound.

Benzethonium chloride is a white powder composed of colorless crystals. It melts at approximately 162° C. It is soluble in water, alcohol, and in chloroform. The monohydrate consists of thin hexagonal plates.

(1) *Safety.* The Panel concludes that there are insufficient data to permit final classification of the safety of benzethonium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzethonium chloride has a low order of toxicity in animals and man and is probably safe in low dosages when used occasionally for short-term therapy. Herrell and Heilman (Ref. 1) tested the toxicity of benzethonium chloride to human leukocytes and found it less injurious than mercurial antimicrobial agents. The $LD_{50}$ in rats orally is 450 mg/kg. Effective concentrations are relatively nonirritating. Ordinarily, salts of quaternary nitrogenous compounds are not lipophilic, are not ionized, and are poorly absorbed through the mucous membranes. The introduction of a highly lipophilic radical into the structure presumably increases the lipid solubility, and penetration through epithelial barriers of cell membranes is enhanced. Systemic absorption therefore is increased, and it is possible for toxic doses to be absorbed from the mucous membranes. Toxic doses can be ingested accidentally, resulting in vomiting, collapse, coma, and convulsions. Quaternary nitrogenous bases ordinarily acting systemically are ganglionic-blocking agents and have a curareform action. Toxic manifestations cause depression of the autonomic nervous system effects and also cause muscle weakness due to a blockade at the myoneural junction. Caution should be exercised when solutions are used for instillation into or irrigating hollow cavities, especially if the solution remains in place for a long time. There is a possibility of absorption of toxic quantities. Adequate data on absorption and attainment of toxic blood levels and the metabolic fate of the "quats" are not available. Data on cumulative effects from continued use on a day-to-day basis over the span of years or a lifetime as would be the case when they are incorporated in mouthwashes are not available. The human fatal dose for quaternary nitrogenous cationic agents has not been established but is believed to be between 1 to 3 g. Although concentrated aqueous solutions are irritant to the skin, percutaneous absorption does not appear to be significant. Benzethonium chloride is absorbed through the mucous membranes of the mouth and throat, but quantitative data from controlled studies are not available. As is the case with other drugs, these agents can act as haptens and cause systemic and local allergic responses. However, the incidence of sensitization is low. No data are available on the mutagenic, tumorigenic, or teratogenic effects of benzethonium chloride when used in mouth rinses or gargles for long-term use on a daily basis for oral health care. There are no data on its effect on the fetus during pregnancy when used daily as a mouthwash.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of benzethonium chloride as an OTC antimicrobial agent for use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzethonium chloride was found to be the most active of a series of chemically allied quaternary ammonium antimicrobial agents studied by Rawlins and associates (Ref. 2). Since that time the pyridinium and quinaldinium compounds have been introduced and this statement, though still correct for the substituted ammonium compounds, is not necessarily applicable to these newer drugs.

Benzethonium chloride was tested by the FDA method on 8 different species of bacteria. These were killed within 5 minutes when concentrations ranging from 1:12,000 to 1:80,000 were used at 20° C in vitro. It was also noted that benzethonium chloride was strongly fungicidal. A 1:1,000 solution killed actinomyces, trichophyton, monilia, and other fungi. Benzethonium chloride has come into rather wide usage as a general germicide and antiseptic for reducing the microbial population of the skin and as an antiseptic for minor

wounds. The most commonly used preparations are 1:1,000 aqueous solutions and a 1:5,000 tincture (alcohol-acetone solution).

The activity of benzethonium chloride, in common with other quaternary nitrogenous antimicrobial agents and in contrast to other types of antimicrobial agents, is greatly lessened or completely nullified by numerous substances. These substances include anionic agents, such as soaps, and a variety of organic substances, such as proteins including blood, pus, and chemicals that act on adsorbents such as cotton. Miller and associates (Ref. 3) observed that this type of antiseptic forms a thin, relatively tough film on skin. The film may be sterile on the exterior but may be holding viable bacteria beneath. One alleged advantage in using benzethonium chloride is that its germicidal activity increases as pH increases. At pH 10, it is several times more active against *Eubacterium typhosa* and *Staphylococcus aureus* than at pH 4.

In a study of the effectiveness of quaternary ammonium compounds on molluscacides, a concentration of 10 parts per million of benzethonium chloride (hyamine 1622) killed all australorbis species of snails (Ref. 4). This fact is of importance from the standpoint of sanitation since these snails serve as the intermediate host of schistosoma. The potential importance of this property is obvious.

A 1:1,000 aqueous solution is available as an antimicrobial agent for use on the skin and mucous membranes. Benzethonium has been recommended as an antiseptic in preoperative and postoperative care of wounds and infected areas and also for application to accessible mucous membranes such as those of the eye, mouth, throat, and the gastrointestinal and genitourinary tracts. Tincture of benzethonium chloride is a 1:500 solution of the ingredient in alcohol and acetone; it is recommended principally for preparation of skin preoperatively and for antepartum preparation of obstetrical patients. A 1:5,000 ophthalmic solution, also containing 2 percent of boric acid, is supplied for use in ocular conditions where an antiseptic is indicated.

The germicidal and detergent properties of benzethonium chloride are utilized for sanitation purposes. It is available in crystalline form for this purpose. Benzethonium chloride is recommended for sanitizing eating and cooking utensils in restaurants, for similar use in dairies, for control of obnoxious odors in public rest rooms, for disinfectant use in laundering operations, for various veterinary germicidal uses, and for controlling algae growth in swimming pools. It is essential, of course, that it be used in proper concentrations for each of these purposes.

Benzethonium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel concludes that, even though benzethonium chloride is effective as an antimicrobial agent in many situations, there are no data from controlled studies that establish it as an effective topical antimicrobial agent for the relief of symptoms of sore mouth or throat or both. Its antimicrobial spectrum is limited and made more so by the uncertainty imposed by environmental factors such as the presence of neutralizing anions, proteins, and organic materials found in the mouth and throat. Furthermore, there is no convincing evidence that the topical application of antimicrobial agents to infected and inflamed areas is of therapeutic benefit. In fact there is evidence that direct, topical application of antimicrobial agents may even aggravate an inflammatory state. (See part IV. paragraph A. above—General Discussion.) The Panel notes that there is no substantial evidence to establish the rationale for using benzethonium chloride on a continuing day-to-day basis as an antimicrobial agent in mouthwashes or rinses when no symptoms of any disease processes are present and in the absence of some obvious prophylactic or therapeutic need.

The Panel concludes that there are insufficient data to justify the use of benzethonium chloride in various mouthwashes, rinses, sprays, or lozenges and other oral health care use (Refs. 5 and 6). (See part IV. paragraph A. above—General Discussion.)

The Panel further concludes that there are insufficient data from controlled studies to establish the effectiveness of benzethonium chloride as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat when used within the proposed dosage limit set forth below.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a0.02- to 0.1-percent concentration of benzethonium chloride in the form of a rinse, mouthwash, or gargle not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1 above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredient. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

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c. *Benzoic acid.* The Panel concludes that benzoic acid is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzoic acid is the simplest carboxy acid of the aromatic series, being a benzene ring with a carboxyl group. It is also known as phenylcarboxylic acid, phenylformic acid, flowers of benzoin, and flowers of benzamine (Ref. 1). Benzoic acid occurs in the free form and as salts in various plants, especially in balsams and resins obtained from coal tar. It also occurs as hippuric acid (benzoyl glycine) in the urine of nearly all vertebrates. Formerly, benzoic acid was obtained from benzoin and hippuric acid. In present-day manufacturing processes, it is synthesized from a variety of starting compounds, such as toluene, benzaldehyde, benzotrichloride etc. (Refs. 1 and 2).

Benzoic acid consists of white crystals, scales, or needles that have a

slight aromatic odor. It is somewhat volatile at warm temperature and in steam. One gram dissolves in about 300 mL water, 3 mL alcohol, 5 mL chloroform, and 3 mL ether. It melts at about 122° C. Benzoic acid may be found free in nature. Gum benzoin may contain up to 20 percent benzoic acid. Most berries contain about 0.5 percent benzoic acid. It has been used as a preservative for foods and cosmetics and has been also used in a concentration of 6 percent in combination with 3 percent salicylic acid as an antifungal agent. It has varying degrees of antimicrobial activity. Benzoic acid is used as a buffering agent and a pharmaceutical necessity in some OTC products. Use of benzoic acid is permitted as a bacteriostatic agent in certain foods and medicinal products (Ref. 3).

(1) *Safety.* The Panel concludes that benzoic acid is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzoic acid alone is a mild irritant to the skin, eyes, and mucous membranes. Gosselin et al. (Ref. 4) rate the toxicity of benzoic acid as 3, which is a low rating. The mean lethal dose ($LD_{50}$) of benzoic acid in dogs and cats is 2 g/kg. In rats the intravenous $LD_{50}$ is 1.7 g/kg. Tremors and convulsions preceded death in poisoned animals.

In one study on toxicity, the oral daily administration of benzoic acid to rats in dosages of 70 to 80 mg/kg caused an increase in mortality, decrease in weight gain, and decrease in resistance to stress (Ref. 5). Additive toxicity was noted when sodium bisulfite, another food preservative, was combined with benzoic acid.

The toxicity of benzoic acid for man has not been established. A 67-kg man ingested doses of 50 g benzoic acid without ill effects. Large oral doses produce gastric pain, nausea, and vomiting. In nine patients treated with 1.5 g benzoic acid twice daily up to a total of 12 g, gastric burning and anorexia resulted, but no renal impairment was observed. When benzoic acid or benzoate are ingested they conjugate with aminoacetic acid (glycine) and appear in the urine chiefly as hippuric acid. This conversion takes place in the liver. The ability to form hippuric acid from benzoic acid has been used as the basis for estimating liver function, particularly the ability of the liver to detoxify chemical substances. Benzoic acid is an irritant to the mucous membranes and cannot be administered internally without manifestations of gastric irritation. The neutral benzoates, on the other hand, are well tolerated in doses of 6 g or more.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of benzoic acid as a OTC antimicrobial agent for topical use on mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzoic acid is effectively germicidal against certain microbial strains. Goshorn, Degering, and Tetrault (Ref. 6) found that at a pH of 3.5, a 1:800-solution of benzoic acid kills both *Escherichia coli* and certain strains of staphylococci within an hour. At a pH of 5, however, it is not certain that benzoic acid is still bactericidal. At a strength of even 1:20 and pH 5, it will kill these organisms. Benzoic acid will inhibit bacterial growth in a concentration of 1:3,000 at this pH. The antimicrobial action of benzoic acid is chiefly, if not exclusively, due to the un-ionized portion of the molecule since benzoate ions permeate living cells with difficulty. A combination of 6 percent benzoic acid and 3 percent salicylic acid in an ointment base, commonly known as Whitfield's ointment, has fungistatic and fungicidal properties. The ointment causes exfoliation of the upper layers of the skin by the keratolytic action of the salicylic acid. A hyperemia characterizes the dermatomycosis and the fungi are cast off with the stratum corneum when the cells desquamate. It is doubtful that the benzoic acid plays an active role in this action since most of the keratolysis is due to the salicylic acid.

Benzoic acid forms salts with sodium hydroxide and other bases. The sodium salt is the most common one in use. Sodium benzoate is ionized, does not penetrate living cell membranes, and is not effective as an antimicrobial agent. the antiseptic activity of sodium benzoate is practically nil. The antiseptic activity of benzoic acid is due to the fact that it is an acid, poorly ionized, lipid soluble, and penetrates living cells.

Reports in the literature published between 1933 and 1950 appear to lend questionable support to the effectiveness of benzoic acid as an individual component in certain preparations used as rinses for the oral cavity (Ref. 7). A report by Barbour and Vincent (Ref. 8) describes the inhibition of *Bacterium aerogenes* and *Aspergillus niger* by benzoic acid. Accumulation of the ingredient at the cell surface with the resultant inhibition of microbial growth was greater with benzoic acid than with phenol and other antimicrobial compounds tested. Since the inhibition is a reversible phenomenon, such drugs are unlikely to exert any lasting influence on the flora of the oral cavity. Moreover, neither of the two organisms is representative of those present in the oral cavity. *Bacterium aerogenes* is seldom found in the mouth in appreciable numbers, and *Aspergillus niger* is not recognized as a constituent of indigenous oral flora.

Another study (Ref. 9) merely suggests that benzoic acid might be more useful as a selective medium to be used to isolate fungi from the air by inhibiting growth of airborne bacteria. This comment appears irrelevant to the effectiveness of benzoic acid in the preparations for use in the oral cavity.

A third report by Baldinger and Nieuwland (Ref. 10) described a study comparing the inhibition of *Bacillus coli* by benzoic acid and a series of alpha phenylsubstituted acids. In general, the latter exerted a greater inhibitory effect. This report is irrelevant as far as data pertaining to the effectiveness of benzoic acid in preparations used as rinses in the oral cavity is concerned.

Goshorn, Degering, and Tetrault (Ref. 6) demonstrated that benzoic acid is less active at alkaline or neutral pH than at acid pH. The test organisms studied were *Escherichia coli* and *Staphlyococcus aureus.*

Wyss and Poe (Ref. 11) studied the comparative efficacy of various antimicrobial agents using the FDA phenol coefficient technique. Benzoic acid had a coefficient of 5.3 against *Salmonella typhosa,* but it was no more active than phenol against *Staphylococcus aureus.* This test procedure, in use in 1931, was modified in 1950 because it did not distinguish between bacteriostatic and bactericidal activity. The modified test is not considered applicable to gargles, mouth rinses, and other preparations used in the oral cavity because it is difficult to simulate the flora commonly found in the oral cavity in vitro.

The Panel concludes from the foregoing data that benzoic acid possesses some bacteriostatic and bactericidal antimicrobial activity.

The Panel, however, concludes that there are insufficient data from controlled studies to establish the effectiveness of benzoic acid as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use of 0.1- to 0.3-percent concentration of benzoic acid in the form of a rinse, mouthwash, or syrup not more than.

three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicriobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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d. *Carbamide peroxide in anhydrous glycerin (urea peroxide).* The Panel concludes that carbamide peroxide is safe, but that there are insufficient data available to permit final classification of its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Carbamide peroxide is a relatively stable complex formed by the union of urea with hydrogen peroxide. The compound is also known as urea hydrogen peroxide. Urea is the diamide of carbonic acid; for this reason the compound is also known as urea carbamide. Other names that have been used for urea hydrogen peroxide in the past are hyperal, perhydrit, and perhydrol urea. Its empiric formula is $CO(NH_2)_2.H_2O_2$ and its molecular weight is 94.0. The hydrogen peroxide content of the molecule is 34 to 35 percent of its total weight. The compound is a white crystalline powder that breaks down, if allowed to stand in air, into urea, oxygen, and water. It decomposes to urea and hydrogen peroxide in aqueous solution. One part carbamide peroxide is soluble in 2.5 parts of water. It is soluble in anhydrous glycerin and the complex is stable in glycerin as long as moisture is excluded. Carbamide peroxide is partly decomposed by alcohol and ether into hydrogen peroxide and urea. It is used for the extemporaneous preparation of hydrogen peroxide in the field, for travelers, etc. (Ref. 1).

Carbamide peroxide releases hydrogen peroxide which is decomposed by hydroperoxidases, peroxidases, and catalase present in the tissues, wounds, and saliva, and in bacteria. Catalase causes the release of atomic or "nascent" oxygen, a strong oxidizing agent which is presumed to exert an antimicrobial action before its conversion to diatomic molecular oxygen ($O_2$). The peroxidases induce rapid conversion of urea hydrogen peroxide to peroxide. Breakdown of the hydrogen peroxide to oxygen and water causes formation of bubbles of gas and foaming. This release of oxygen foam accounts for the debriding effect of peroxides. The urea exerts no significant proven therapeutic effect. In addition to anhydrous glycerin, carbamide peroxide is also soluble in propylene glycol.

(1) *Safety.* The Panel concludes that carbamide peroxide is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Although data on the safety of carbamide peroxide is sparse, it is the consensus of the panel that carbamide peroxide is safe. There were no data available in standard textbooks references in the literature, or in Panel submissions on acute, subacute, or chronic studies in animals or humans (Refs. 2, 3, and 4). There are no available data on irritation and hypersensitivity reactions, teratogenicity, or carcinogenicity attributed to the compound. One manufacturer presented evidence from 3,000 prescriptions and claimed that there were no adverse reactions in humans from use of the preparation. This was the only human study concerning adverse or toxic reactions (Ref. 5).

The Panel acknowledges that urea is a naturally occurring substance in the body, and that hydrogen peroxide, in concentrations of less than 3 percent, is safe for use in the mouth and throat. The Panel also recognizes that as soon as the combination of urea and peroxide comes in contact with living tissues, it is decomposed into urea and hydrogen peroxide. The Panel therefore, concludes that it is safe.

Since urea hydrogen peroxide is combined with glycerin, the Panel has made its judgment on the preparation dissolved in anhydrous glycerin. Clinical use and marketing experience has confirmed that carbamide peroxide in glycerin is safe in the dosage form proposed for use in the oral cavity.

There are reportred clinical studies in which the carbamide peroxide inanhydrous glycerin was used in inflammatory and otic conditions. It was found to be nontoxic, nonirritating, and nonsensitizing, and no adverse reactions were reported. Carbamide peroxide has been used in animals with no reported toxicity or irritation. However, the Panel cautions that concentration of hydrogen peroxide are toxic to the soft tissues and the oral cavity, and that rapid release of hydrogen peroxide from urea hydrogen peroxide could be toxic locally.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of carbamide peroxide as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The proposed antimicrobial mechanism of action of carbamide peroxide is that it releases hydrogen peroxide. This is discussed in detail elsewhere in this document (See part IV. paragraph B.3.m. below—Hydrogen peroxide.)

Urea is a product of protein metabolism and allegedly aids in debriding necrotic tissues. Urea is a waste product that is found in human urine in concentrations of about 2 percent. It is a white, pure crystalline

material that is odorless and nontoxic. It was the first organic substance synthesized. A 2-percent solution has been recommended for treating external suppurating wounds. Urea allegedly prevents infections and stimulates cleansing and healing. However, data to substantiate this claim are lacking.

The Panel concludes that these are insufficient data available from controlled studies to establish the effectiveness of carbamide peroxide as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 9.0- to 15.0-percent concentration of carbamide peroxide in anhydrous glycerin or propylene glycol in the form of drops or as a swab. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B. 3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care anitmicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Windhoz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1266, 1976.

(2) OTC Volume 130037.

(3) OTC Volume 130085.

(4) OTC Volume 130017.

(5) OTC Volume 130016.

(6) Harvey, S.C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 997, 1975

e. *Cetalkonium chloride.* The Panel concludes that cetalkonium chloride is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Cetalkonium chloride ($C_{25}H_{46}ClN$) is also known as cetyldimethylbenzylammonium chloride, N-hexadecyl-N,N-dimethylbenzenemethanaminium chloride, benzylhexadecyldimethylammonium chloride, and hexadecyldimethylbenzylammonium chloride. Cetalkonium chloride has a molecular weight of 396.12.

Cetalkonium chloride is soluble in water, alcohol, acetone, ethyl acetate, propylene, and carbon tetrachloride. The pH of the aqueous solution is 7.2. Cetalkonium chloride is a cationic quaternary ammonium surfactant which is used as an antibacterial agent and fungicide. It is used in leather processing, textile dyeing, and as a mildew preventive in silicone-based water repellents. It is comparable with many nonionic detergents and is active in moderately alkaline solutions. Cetalkonium chloride water is odorless and practically tasteless at a 1:2,000 dilution (Ref. 1).

(1) *Safety.* The Panel concludes that cetalkonium chloride is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

Studies included in a product submission have demonstrated that cetalkonium chloride, in a dose of 5 mg/kg, had a depressor effect upon the blood pressure of three dogs anesthetized with sodium barbital (Ref. 2). The prior injection of atropine apparently had no inhibitory effect on the vasodepression produced by the drug. Single intravenous doses of cetalkonium chloride equal to 17.3 and 20 mg/kg were toxic to 50 percent of the animals when tested in mice and rats, respectively. Cetalkonium chloride was found to have an oral $LD_{50}$ value of 725 ± 20 mg/kg in the mouse and 990 ± 91 mg/kg in the rat. Subacute toxicity tests were carried out in mice, rats, and rabbits for periods of 14 days. It was concluded that cetalkonium chloride was more toxic by repeated administration than by single dose. Chronic toxicity studies were carried out in dogs for 14 weeks. Cetalkonium chloride retarded growth slightly, but no hematologic or pathologic changes which could be attributed to medication with the drug were observed. Solutions of cetalkonium chloride of 1:1,000 were found to be nonirritating to the bladder mucosa and oral mucosa of rabbits. Dilutions of 1:2,000 to 1:4,000 instilled into the rabbit eye produced mild to moderate irritation. The following morning, the eyes were still slightly irritated. In three cases the 1:3,000 dilution produced a mild irritation, but all eyes appeared normal the following morning. The 1:4,000 dilution produced a mild irritation in one rabbit, and only a slight irritation in two other rabbits. It appeared to be normal the following morning.

Data on tumorigenic, mutagenic, and teratogenic effects after long-term use in mouthwashes, gargles, and rinses are not available. Data on teratogenic effects on daily use of mouthwashes during pregnancy are not available.

(2) *Effectiveness.* The Panel concludes that there are insufficient data to permit final classification of the effectiveness of cetalkonium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

Industry researchers in a study incorporated in a submission to the Panel performed both in vitro and in vivo testing of cetalkonium chloride (Ref. 2). Samples of saliva were collected from several normal human subjects, pooled, and warmed to 37° C. Samples of 0.5 mL of saliva were transferred to sterile culture tubes and 2mL of undiluted mouthwash, previously warmed to 37° C, were added. The final concentration of saliva was 20 percent. Subcultures were made at intervals of 15, 30, 60, 90, 120, and 300 seconds after the addition of the mouthwash. They reported that normal saliva failed to show growth of bacteria after 15 seconds exposure to the cetalkonium chloride mouthwash. These results are open to criticism in that pooled saliva cannot be standardized from laboratory to laboratory and, therefore, should not be used. In addition, no inactivating medium was used as recommended in the in vitro test suggested by the Panel. The same authors, in order to compare cetalkonium chloride to other nonquaternary mouthwashes under conditions of actual use, carried out experiments on normal subjects to measure the percentage reduction of bacteria in the mouth following the use of various mouthwashes. According to these authors, cetalkonium chloride produced a reduction of over 90 percent in the number of flora in the oral cavity for at least 30 minutes after medication. These results are also open to criticism because no inactivating medium was used as recommended in the in vitro test suggested by the Panel.

Cetalkonium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

Much of the literature forwarded to the Panel in the form of industry submissions was not pertinent to cetalkonium chloride (Ref 2).

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of cetalkonium chloride as

an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 253, 1976.

(2) OTC Volume 130073.

f. *Cetylpyridinium chloride.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of cetylpyridinium chloride as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Cetylpyridinium chloride is a quaternary nitrogenous compound derived from pyridine (Ref 1). Pyridine is a six-membered heterocyclic structure containing a trivalent nitrogen atom at the number one position in the ring. Conversion of the nitrogen atom to a pentravalent state permits addition of a hexadecylradical or other side chain and a hydroxyl, chloride, or bromide anion to the nitrogen atom, forming quaternary nitrogenous compounds. These are referred to as pyridinium derivatives. They have five bonds, four negative that form covalent bonds with organic radicals and one positive that results in an ionic type of bonding. (See part IV. paragraph A.8.b. above—The pyridinium compounds.)

A hexadecyl (cetyl) radical is substituted for a hydrogen atom on position one and a hydroxyl group bonds with the positive charge to form a base. When dissolved in water, it ionizes into a quaternary pyridinium ion and a hydroxyl ion. It interacts with acids such as hydrochloric to form salts. The chloride is a commonly used salt. Cetylpyridinium chloride is 1-hexadecylpyridinium chloride and contains, on the anhydrous basis, not less than 99 percent of $C_{21}H_{38}ClN$, it may be prepared by interaction of cetyl chloride and pyridine under pressure at an elevated temperature (Ref 2).

Cetylpyridinium chloride is a white powder, with a slight, characteristic odor (Ref 2). The salt is available as the monohydrate. Cetylpyridinium chloride melts at from 77 to 82° C. It is freely soluble in water, alcohol, chloroform, but it is not soluble in ether and benzene (Ref 3). A 1-percent solution is neutral to litmus, but when pH is determined with a glass electrode, it ranges between 6 and 7. The surface tension of a 0.1-percent aqueous solution at 25° C is 43 dyn/cm, a 1-percent aqueous solution is 41 dyn/cm, and a 10-percent aqueous solution is 38 dyn/cm (Ref 3).

The cetyl radical confers lipophilic qualities to the compound as is the case with multicarbon radicals in other quaternary nitrogenous compounds. This sets the balance between the lipophilic-hydrophilic attributes of quaternary nitrogenous compounds necessary for antimicrobial activity.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of cetylpyridinium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The minimum lethal does for cetylpyridinium chloride in rabbits tested by injection was 20 mg/kg, and the average lethal does was found to be 35 mg/kg (Ref. 4). It is more toxic when instilled intraperitoneally (Ref 4). The $LD_{50}$ is 250 kg/mg subcutaneously, 6 mg/kg intraperitioneally, 30 mg/kg intravenously, and 200 mg/kg orally (Ref 5). When 50 mg/kg in water were administered daily for 60 days to rats, no toxic effects or alteration in the rate of growth of the animals were noted (Ref 5). Doses of 5 to 10 mg/kg administered through the esophagus showed no toxic effects over a 60-day period (Ref 5).

The toxic systemic effects of cetylpyridinium chloride are similar to those of other quarternary nitrogenous compounds and are described below.

A 1:3,000 solution of cetylpyridinium is irritating to the mucous membranes of the conjunctiva, but not when applied to the skin (Ref. 6). A 1:200 alcoholic or aqueous solution of cetylpyridinium does not cause skin irritation (Ref. 7). Although concentrated aqueous solutions are primarily skin irritants, percutaneous absorption is not believed to be significant (Ref. 8). Allergic manifestations have not been reported, but the Panel warns that the cetylpyridinium chloride can act as a hapten and cause sensitization.

The human fatal dose for the quaternary nitrogenous compounds has not been established, but has been estimated to be between 1 and 3 g for an adult (Ref. 8). Toxic doses of cetylpyridinium chloride manifest an autonomic (nicotinic) blocking effect on the ganglia and a curariform (muscarinic) type of response. The principal manifestations of poisoning from oral ingestion are vomiting, collapse, and coma (Ref. 8). Local gastrointestinal irritation, restlessness, apprehension, confusion, dyspnea (labored breathing), and cyanosis occur followed by convulsions, muscle weakness or paralysis, and death due to paralysis of respiratory muscles (Ref. 8). The nicotine-like effects of blocking the autonomic ganglia are most likely due to the curariform action and are similar to those manifested by many quaternary nitrogenous compounds (Ref. 9). Ordinarily, salts of quaternary nitrogenous compounds do not penetrate epithelial barriers because they are not lipophilic and are highly ionized. The presence of a high molecular weight lipophilic group on the molecule of these quaternary nitrogenous compounds increases their lipid solubility and facilities penetration through cell membranes. The lipophilic group enhances its degree of absorption.

Data on cumulative effects, metabolism, and excretion of cetylpyridinum chloride in man, particularly after long-term use, are not available. Data on tumorigenic, mutagenic, and teratogenic effects when used on a daily basis for months or years in mouthwashes and other oral health care products are not available. Data on teratogenic effects if used during pregnancy are not available. Clinical experience following prescription and OTC use of the ingredient have not thus far revealed any overt toxic manifestations.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness cetylpyridinium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Cetylpyridinium chloride has the same detergent and antiseptic actions characteristic of other quaternary nitrogenous compounds, i.e., benzalkonium chloride and benzethonium chloride, that manifest antimicrobial activity (Ref. 2). The compound was introduced for clinical

use in 1942. Cetylpyridinium chloride is bactericidal and bacteriostatic against may gram-positive and some gram-negative organisms. A 1:50,000 aqueous solution will kill staphylococci in 10 minutes, though not in 5 minutes (Ref. 10). It is also active against some fungi, including *Candida albicans,* and against *Trichomonas vaginalis* (Ref. 2). Cetylpyridinium chloride's action is uncertain or it is ineffective against spores and most viruses. Its activity is diminished by the presence of serum, tissue fluids, proteins, lipids, and phospholipids (Ref. 2). Soaps, other anionic sufactants, and detergents are incompatible with cetylpyridinium chloride and antagonize its action (Ref. 2). Cetylpyridinium Chloride lowers surface tension and has wetting and emulsifying properties similar to other quaternary nitrogenous compounds (Ref. 2).

When applied to the skin, cetylpyridinium chloride and other quaternary ammonium antiseptics form a film under which bacteria may remain viable even though the outer surface of the film is bactericidal and sterile (Ref. 2).

Cetylpyridinium chloride in a concentration of 1:100 is used topically for preoperative disinfection of intact skin. A 1:100 solution has been used for prophylactic antisepsis of superficial wounds. A 1:5,000 to 1:10,000 solution has been used for therapeutic disinfection of mucous membranes. Cetylpyridinium chloride is used as an active ingredient in mouthwashes, rinses, and gargles. It is also incorporated into lozenges with the intent of obtaining an antimicrobial action on the mucous membranes of the mouth and throat (Ref. 2).

The antimicrobial spectrum of cetylpyridinium chloride is limited. This is made more so by the uncertainty imposed by environmental factors during use, such as the presence of proteins, neutralizing anions, and organic material and debris in the mouth. Furthermore, there is sufficient evidence from long-term clinical experience that the topical application of antimicrobial agents to infected and inflamed areas is of doubtful therapeutic value, is not curative, and may even aggravate an inflammatory state. The Panel notes that there are no data to justify the use of cetylpyridinium choride in oral health care products on a continuing day-to-day basis for protracted periods of time for prophylaxis and other uses when no symptoms are present and no therapeutic benefit can be demonstrated. The Panel concludes that even though cetylpyridinium chloride does kill or inhibit certain select microorganisms found in the oral flora, there are insufficient data to demonstrate that this antimicrobial activity is of therapeutic benefit in treating sore mouth or sore throat or both.

Cetylpyridinium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of cetylpyridinium chloride as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.025- to 0.1-percent concentration of cetylpyridinium chloride in the form of a rinse, mouthwash, or gargle not more than three to four times daily. Use a 0.025- to 0.1-percent concentration of cetylpyridinium chloride in the form of a lozenge every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling).

(5) *Evaluation.* Data to demontrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 148, 1957.

(2) Osol, A., et al., "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., J. B. Lippincott Co., Philadelphia, p. 259, 1960.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 254, 1976.

(4) OTC Volume 130007.

(5) Nelson, J. W., and S. C. Lyster, "The Toxicity of Myristyl-gamma-Picolinium Chloride," *Journal of American Pharmaceutical Association (Scientific Edition),* 35:89–94, 1946.

(6) Warren, M. R., et al., "Pharmacological and Toxicological Studies on Cetylpyridinium Chloride, A New Germicide," *Journal of Pharmacology and Experimental Therapeutics,* 74:401–408, 1942.

(7) Clarke, G. E., "Skin Sterilization With Cetyl Pyridinium Chloride," *The Urologic and Cutaneous Review,* 46:245–246, 1942.

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(9) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, section III, pp. 197–200, 1969.

(10) Kolloff, H. G., et al., "Germicidal Activity of Some Quaternary Ammonium Salts," *Journal of the American Pharmaceutical Association (Scientific Edition),* 31:51–53, 1942.

g. *Chlorophyll.* The Panel concludes that chlorophyll is safe, but that there are insufficient data available to permit final classification of the effectiveness of chlorophyll as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Chlorophyll is the green pigment and photosynthetic agent found in plants. Functionally, it is comparable to hemoglobin found in animal life in that it sustains respiration in plants. Chlorophyll is not a single entity, but is found in three forms: a, b, and c. Higher phyllogenetic orders of plants with green leaves and green algae contain chlorophyll a and chlorophyll b in the approximate ratio of 3:1. Chlorophyll c is found together with chlorophyll a in many types of marine algae.

Chlorophyll a is freely soluble in ether, ethanol, acetone, chloroform, carbon disulfide, and benzene. The alcoholic solution is blue-green with a deep red fluorescence (Ref. 1). Chlorophyll b is freely soluble in absolute alcohol and ether. The ether solution has a brilliant green color. Solutions with other organic solvents are usually green to yellowish-green with red fluorescence (Ref. 2).

The chlorophyll of commerce is an intensely dark-green aqueous, alcoholic, or oil solution. It is made from dehydrated alfalfa and broccoli leaves.

Careful alkaline hydrolysis of chlorophyll replaces the methyl and phytyl ester groups with sodium or potassium. The resulting salts are called chlorophyllins and are water soluble. Water-soluble sodium and potassium salts occur as a blue-black glistening powder having a fishy odor. They are slightly soluble in alcohol and freely soluble in water. A 1-percent solution in water is dark green and alkaline, having a pH range of 9.5 to 10.7.

Chlorophyll was introduced into clinical medicine in 1945. It is similar to hemoglobin, structurally different in that magnesium replaces iron in the complex of the pyrrole rings. Chlorophyll and its derivatives are used to color soaps, oils, fats, waxes, confectionery, preserves, liquors, cosmetics, and perfumes. It is also used as a deodorant.

The Panel reviewed a submission on a currently marketed product which contained both safety and effectiveness data on chlorophyll (Ref. 3).

(1) *Safety.* The Panel concludes that chlorophyll is safe as an OTC antimicrobial agent for topical use on mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Cholorphyll and its derivatives have little or no toxicity when applied topically, taken orally, or injected intravenously (Ref. 4). Chlorophyll is found in all green-colored plant life, and inasmuch as leaves and grasses serve as food and are consumed in large quantities in the diets of herbivorous and omnivorous animals, it is not unreasonable to assume that chlorophyll is nontoxic when used topically, orally, or intravenously. A potassium-sodium-copper complex of chlorophyll fed to rats in a concentration of 3 percent of their diets for life showed no signs of toxicity for the complex including copper (Ref. 5). Sensitization has not been reported following its use topically or when ingested orally.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of chlorophyll as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Chlorophyll has been used in aqueous solutions as a deodorant to overcome mouth odor. The mechanism of its alleged action as a deodorant has never been clearly defined, and the ingredient has fallen into disuse over recent years since it has not been demonstrated that it is an effective deodorant. In dogs, doses of 30 to 150 mg decreased halitosis; however, the ingested chlorophyll had no effect on the odor in the dogs' coat (hair) in the animals tested. It allegedly promotes wound healing, but no data were submitted or are available from controlled studies to substantiate that this occurs.

The water-soluble chlorophyllins appear to have some bacteriostatic properties in vitro. The concentration necessary for this inhibition is often 1:80 or more; however, all pathogens are not affected to the same degree. In vivo, the bacteriostatic influence of these chlorophyllins is supposedly due to the production of an unfavorable environment rather than to a direct action of the agent on the metabolic activity or cell structure of the pathogens (Ref. 4).

There is no evidence that chlorophyll derivatives are bactericidal. Insufficient data were submitted concerning the effectiveness of chlorophyll as an antimicrobial agent for the relief of symptoms of sore mouth and sore throat.

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of chlorophyll as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.2- to 0.5-percent concentration of chlorophyll in aqueous solution in the form of rinses, mouthwashes, gargles, sprays, or swabs not more than three to four times daily. Use a 0.2- to 0.5-percent concentration of chlorophyll in the form of a tablet or lozenge every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Anderson, A. F. H., and M. Calvin, "An Improved Method for the Separation and Purification of Chlorophyll a," *Nature,* 194:285-286, 1962.

(2) Dougherty, R. C., et al., "Structure of Chlorophyll c," *Journal of the American Chemical Society,* 88:5037-5038, 1966.

(3) OTC Volume 130015.

(4) Dobbs, E. C., "Pharmacology and Oral Therapeutics," 11th Ed., C. V. Mosby Co., St. Louis, p. 422, 1956.

(5) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 1629, 1955.

h. *Dequalinium chloride.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of dequalinium chloride as OTC antimicrobial ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Dequalinium is a base derived from 2-methylquinoline. Methylquinoline may be quaternized to form a series of quinaldinium compounds. When the trivalent nitrogen is converted to the pentavalent form, a hydrogen atom on the nitrogen atom of the quinaldine base may be substituted by an alkyl radical. In dequalinium, a nitrogen atom is attached at each end of a decamethylene chain. Thus, the dequalinium molecule has two quaternary nitrogen atoms, one at each pole of the chain. This chain serves as the lipophilic portion of the molecule. The two quinaldinium groups at each end are ionized into quaternary cations. Dequalinium, therefore, is similar in chemical, physical, and pharmacologic properties to other quaternary nitrogenous compounds.

Dequalinium acetate is 1,1'-decamethylenebis(4-aminoquinaldinium acetate); dequalinium chloride is the chloride of the same quaternary base (Ref. 1). It is a white or pinkish-buff, slightly hygroscopic powder. One gram dissolves in about 2 mL water and in 12 mL alcohol. It melts, with decomposition, at about 280°C.

Dequalinium chloride is a creamy-white powder. It is slightly soluble in water (1 g in 20 mL). One gram dissolves in about 200 mL propylene glycol. It melts, with decomposition, at about 315°C.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of dequalinium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Dequalinium has a low degree of toxicity similar to other "quats." The lethal dose for humans is not known, but is believed to be from 3 to 5 g. No data on acute animal or chronic toxicity in humans were submitted to the Panel. The incidence of sensitization is low. Concentrated solutions can be irritating to the skin. Data on its absorption from the mucous membranes, metabolic fate, or excretion are not available. The Panel was not furnished with data from controlled studies concerning tumorigenic, mutagenic, or teratogenic effects when used on a daily basis in the mouth and throat for months or years at a time in mouthwashes and similar oral health care products. No data are

available on teratogenic effects when used during pregnancy.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of dequalinium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Dequalinium acetate and chloride are antibacterial and antifungal agents. They are active against many gram-positive and gram-negative bacteria, also against *Borrelia vincenti, Candida albicans,* and several trichophyton species. Their activity is little affected by serum.

The chloride is applied locally in a variety of preparations (Ref. 2). For infections of the mouth, gums, and throat, it is used in lozenges containing 0.25 mg, or applied as a 0.5-percent paint in propylene glycol. For monilial or trichomonal vaginitis it is employed in pessaries containing 10 g. For infected skin lesions, burns, or wounds, a cream containing 0.4 percent of dequalinium chloride is applied; 0.25 percent of prednisolone may be added. Dequalinium acetate, which is much more soluble in water, is used in medicated gauze dressings.

The dequalinium salts are incompatible with soap and other anionic surface-active agents; they are also incompatible with phenol and chlorocresol.

The Panel has no submission from any firm of any product containing either of these salts. The Panel feels that dequalinium chloride is of limited clinical usefulness as a topical antimicrobial agent for the temporary relief of occasional symptoms of sore mouth or throat because its antimicrobial spectrum is limited and made more so by the uncertainty imposed by environmental factors such as the presence of proteins, neutralizing anions, and organic material in the mouth. Furthermore, the evidence is overwhelming that the topical application of antimicrobial agents to infected an dinflamed areas is of doubtful therapeutic value, is not necessarily curative, and may even aggravate an inflammatory state. Antimicrobial agents are of value for certain infections for which the agent is specifically microbicidal. Such special conditions can only be diagnosed by a physician or dentist and are not amenable to self-diagnosis or treatment such as would be the case for OTC products.

Dequalinium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel does not recommend mouthwashes, rinses, sprays, or lozenges containing antimicrobial agents for deodorizing, cleansing, or prophylaxis, or for oral health care on a daily basis or for use for protracted periods particularly in situations that are devoid of symptoms. (See part IV. paragraph A.2. above—Antimicrobial agents for use in the oral cavity.)

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of dequalinium acetate and chloride as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.5-percent solution of dequalinium chloride in propylene glycol. Apply by swabbing locally to lesions in the mouth and throat not more than three to four times daily. Use a lozenge containing 0.25 mg of dequalinium chloride every 2 hours if necessary. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above-Cateogory I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care animicrobial agents. (See part IV. pargraph C. below—Data Required for Evaluation.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ. p. 381, 1976.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 396, 1973.

i. *Domiphen bromide.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of domiphen bromide as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Domiphen is a quaternary ammonium compound. It is a base that forms salts with acids. The bromide is the salt used for antimicrobial purposes. Chemically it is N,N-dimethyl-N-(2-phenoxyethyl-1-dodecanaminium bromide; dodecyldimethyl (2-phenoxyethyl) ammonium bromide; (beta-phenoxyethyl) dimethyldodecylammonium bromide, ($C_{22}H_{40}BrNO$) (Ref. 1). Domiphen bromide is a white crystalline substance. The crystals have a mild, characteristic odor, a bitter taste, and are freely soluble in water (100 g/mL). Domiphen bromide is soluble in alcohol, acetone, and chloroform, but only slightly soluble in benzene. At 25° C the pH of a 10.0-percent aqueous solution is 6.42, the 1.0-percent solution 5.5, and the 0.1-percent solution 6.8. As is the case with other quaternary nitrogenous compounds, salts of domiphen are surface-active agents with detergent and surface tension-reducing properties. The salts ionize when dissolved in water and the cation is the active ion. The surface tension value of the 10-percent aqueous solution at 25° C is 26.75 dyn/cm and the 0.1-percent 22.08 dyn/cm. Aqueous solutions are clear and colorless and foam profusely on shaking. Solutions are incompatible with anionic agents, particularly soaps.

Domiphen bromide is a member of a large group of quaternary ammonium surface active compounds. They were widely used as disinfectants for inanimate objects but subsequently lost popularity as their limitations became apparent. To a lesser extent, certain members of the group have been used as skin antiseptics. Benzalkonium chloride, U.S.P., is probably the "quat" most extensively employed for this purpose, especially as a preoperative skin preparation prior to minor surgical procedures. The antimicrobial activity of the "quats" has been extensively reviewed by Lawrence and Block (Ref. 2).

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of domiphen bromide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The concentrations of domiphen bromide used in commercial lozenges and mouthwashes appear to be nontoxic. Kutscher and Budowsky (Ref. 3) stated that clinical use of a mouthwash containing 0.01 percent domiphen bromide two to six times daily for up to 52 weeks resulted in no apparent local or systemic toxicity.

There were 746 patients treated with this or other regimens of the same solution.

No local or systemic toxicity was attributable to 0.01-percent domiphen bromide when used as a mouth spray in 154 patients. The patients were all being treated for oral disease, and the duration of therapy varied from 2 to 42 days. An unspecified number of patients was placed on oral rinses 2 to 6 times per day for up to 52 weeks using 0.01 percent domiphen bromide solution. No toxicity was reported during or after this therapy (Ref. 3).

Patch-tests utilizing 1:1,000 solutions of domiphen bromide applied to the skin of 405 volunteers were negative after being in place for 24 hours. The solvent for domiphen bromide was not specified. These same individuals were retested 10 days later and again the responses were all negative (Refs. 4 and 5).

Six adverse reactions were reported between 1958 and 1970 for a lozenge product containing domiphen bromide. These included one complaint of lack of effectiveness. Other complaints included burns on the tongue (two cases), soreness of the mouth (one case), fungal growth after use (one case), and chalk-like taste (one case) (Ref. 5).

A number of animal studies have been conducted with regard to the safety of domiphen bromide. An unpublished study (Ref. 6) determined the intravenous $LD_{50}$ for domiphen bromide to be 18 mg/kg for rats, 31 mg/kg for mice, and 11 to 12 mg/kg for rabbits. The intraperitoneal $LD_{50}$ was 40 to 45 mg/kg for rats and 10 to 20 mg/kg for guinea pigs. The oral $LD_{50}$ could not be determined since marked diarrhea resulted. Oral doses used were as high as 800 mg/kg with five of six unspecified laboratory animals surviving (Ref. 7). The pharmacological and toxicological effects of the various quaternary ammonium compounds are almost identical (Ref. 2). Toxic effects can be generalized and result in convulsions or produce central nervous system depression followed by death. The depression is due to the curare-like action of these compounds (Ref. 8).

The movement of frog cilia was inhibited after a 30-minute exposure to a 1:5,000 concentration of domiphen bromide. Daily instillation of a 1:5,000 solution in rabbit's eyes for 17 days resulted in no vasodilation of conjunctival vessels, no change in corneal reflex, and no histological abnormalities (Ref. 9).

Domiphen bromide was administered to white rats of both sexes by gastric intubation for 7 weeks. The dosage was 10 mg/kg daily for 5 days in each week. The animals showed an inability to gain weight comparable to litter-mate controls. No change was found in hematocrit values, red or white blood cell counts, or in the normal distribution of white blood cells. Also, no change in gut flora was found. No changes were found in the liver, kidney, adrenal, bone marrow, brain, heart, lung, spleen, thyroid, pituitary, ovaries, testes, pancreas, skeletal muscle, or retina (Ref. 7).

Six dogs were given domiphen bromide orally for 3 months. One group of three dogs was given 10 mg daily for 5 days per week. A second group of three dogs was given an escalating dosage of 5 mg/kg, then 20 mg/kg, and then 30 mg/kg. A control group was maintained. Vomiting and loss of appetite were noted at the higher doses. One dog demonstrated an atypical reduction in hemoglobin, hematocrit, and an erythrocyte count. No other toxicity or histopathologic changes were induced (Ref. 10).

There are no data from controlled studies on the tumorigenic or mutagenic effects of domiphen bromide when used in the mouth and throat on a regular basis for months and years as a mouthwash or for similar oral health care products. There are no data on its teratogenic effects if used during pregnancy.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of domiphen bromide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There are many reports in the medical literature on the use of domiphen bromide as a skin disinfectant, for disinfecting raw sewage, and as an antimicrobial for use in the oral cavity. These studies, however, are in many cases subjective and uncontrolled. In the studies relevant to the use of domiphen bromide in the oral cavity, the exposure time at the stated concentration is unlikely to occur in the mouth because of salivary dilution.

Sturzenberger and Leonard (Ref. 11) evaluated the effects of a mouthwash containing domiphen bromide and cetylpyridinium chloride in combination on plaque reduction. Twenty-seven adults used their own toothbrush techniques in combination with a 30-second rinse of either the experimental or placebo mouthwash after brushing. After 1 week the experimental mouthwash showed a 38-percent decrease in stainable plaque as compared to either the placebo or a third mouthwash containing the cetylpyridinium chloride only. The Panel emphasizes that it is highly debatable that there is any well-established correlation between plaque reduction and antimicrobial activity in the mouth and does not consider these studies of significance as applicable to relief of the symptoms due to sore throat and sore mouth. This study also does not support the effectiveness of domiphen bromide because domiphen bromide was not tested as a single ingredient.

Gjermo, Baastad, and Rolla (Ref. 12) found that the plaque-inhibiting effects of the quaternary ammonium compounds in vivo did not correlate with their activity against salivary bacteria in vitro.

Shern, Swing, and Crawford (Ref. 13) compared the in vitro antimicrobial effects of chlorhexidine, a quaternary ammonium compound, with other surface-active compounds. They used the in vitro plaque assay system of McCabe, Keyes, and Howell (Ref. 14) to determine the minimum concentration of drug necessary to inhibit plaque formation by *Streptococcus mutans* and gram-positive filamentous strains. The quaternary ammonium compound benzalkonium chloride was approximately equal in plaque-inhibitory ability to chlorhexidine gluconate and significantly more effective than other compounds tested. As stated above the Panel does not regard these studies as proof of effectiveness of antimicrobial activity in the mouth.

Turesky, Glickman, and Sandberg (Ref. 15) evaluated the antiplaque effects of the quaternary ammonium compounds. These substances inhibited plaque growth. Saliva or pellicle did not affect the products' antibacterial activity.

Seidenberg (Ref. 16) demonstrated that domiphen bromide was effective as a skin disinfectant when the hands were washed for a 3-minute period in a 0.1-percent aqueous solution. Domiphen bromide was bactericidal at low levels against *Escherichia coli,* salmonella species, *Shigella dysenteriae, Staphylococcus aureus, Streptococcus hemolyticus,* and *Diplococcus pneumoniae.* Gram-positive bacteria were more sensitive than gram-negative strains and proteus species were resistant. It was noted that soaps and serum proteins markedly reduced the activity of domiphen bromide. This study by Seidenberg (Ref. 16) was carried out using a 0.1-percent solution of the same product which apparently represented a 1:1,000 concentration of domiphen bromide. This is 10 times the concentration of domiphen bromide in

the lozenge product and 20 times that contained in two other mouthwash products. For this reason this study is not relevant to the effectiveness of domiphen bromide as an antiseptic contained in mouthwashes or lozenges. The concentrations of domiphen bromide tested in vitro varied from experiment to experiment with no consistent protocol. However, when protein was present in the broth medium, a concentration of 0.015 percent (1:6,666) domiphen bromide was required to kill certain gram-positive bacteria, e.g., *Diphtheria bacilli,* and 2.5 percent (1:40) was necessary to kill certain gram-negative bacteria (Ref. 16). Currently marketed mouthwashes contain 1:20,000 domiphen bromide. The findings of Seidenberg (Ref. 16) do not support the antiseptic effectiveness of domiphen bromide.

Kutscher et al. (Ref. 17) studied the effect of domiphen bromide on 18 pathogenic strains of *Candida albicans.*

After 17 hours of incubation, 3 of the 18 strains were inhibited by a 1:48,000 dilution of the compound, 2 of the 18 strains were inhibited by a 1:96,000 dilution, 12 of the 18 strains were inhibited by a 1:192,000 dilution, and 1 of the 18 strains was inhibited by a 1:384,000 dilution. The authors stated that an optimistic outlook on the possible clinical usefulness of domiphen bromide was justified on the basis of their results. The findings of Kutscher et al. (Ref. 17) of merely inhibiting *Candida albicans* by a 17-hour exposure to low concentrations of domiphen bromide has dubious signifiance relative to its generalized use as a mouthwash. While this yeast is a component of the indigenous oral flora, it is normally present in large numbers. Moreover salivary flow would certainly dilute the 0.005-percent (1:20,000) concentration of domiphen bromide found in commercially available mouthwash 10 times to 1:200,000 within 17 hours or less.

Scala and Vicari (Ref. 18) found the growth of *Stapylococcus aereus* to be inhibited for 48 hours by a 0.8 μg/mL concentration of domiphen bromide. A 1.2 μg/mL concentration inhibited the same organism for 72 hours. A concentration of 1.2 μg/mL also inhibited the growth of *Escherichia coli* for 72 hours. The inhibitory concentration indicated in this study for both organisms is approximately 1.0 μg/mL (0.001 mg/mL=1:1,000,000). Moreover, a 48- to 72-hour exposure time to such a concentration is unlikely to occur in the mouth because of salivary dilution.

Bavin, Kay, and Simmonite (Ref. 19) compared the antibacterial activity of domiphen bromide to other quaternary ammonium compounds and disinfectants. They found domiphen bromide to have a level of activity that is either equal to or better than benzalkonium chloride against *Staphylococcus aureus, Proteus vulgaris, Salmonella typhi, Klebsiella pneumoniae, Bacillus mycoides, Pseudomonas aeruginosa,* and *Clostridium tetani.* The bacterium which was least sensitive to domiphen bromide and the other quaternary ammonium compounds was *Pseudomonas aeruginosa.* The concentrations of domiphen bromide and the other quatenary ammonium compounds needed to kill the test bacteria increased when 10-percent serum was incorporated into the nutrient broth. However, the concentration of domiphen bromide needed to inhibit growth was less than benzalkonium chloride for all organisms except *Staphylococcus aureus* and *Bacillus mycoides.* In regard to these two bacterial strains, domiphen bromide was at least as active as the rest of the quaternary ammonium compounds. In a summary of their work, Bavin, Kay and Simmonite (Ref. 18) indicated domiphen bromide to be the most active of the different antiseptics which they studied. Partial inactivation occurred in the presence of soap or protein. This study, which was fairly well designed, took into account the need to utilize a large inoculation ($10^7$ microorganisms per test), the addition of particulate organic material to the domiphen bromide prior to exposure of the test organism and the use of an inactivator in the subculture medium employed to ascertain the bacterial activity. The use of the inactivator, polyethylene oxide, was not significant in the test results. This is not surprising because, since the paper's publication, better inactivators have been found. The addition of particulate organic material (killed yeast cells) to the test system demonstrated a reduction in the bactericidal activity of domiphen bromide of about 20- to 40-fold. With a 10-minute exposure, the bactericidal concentrations ranged from 100 mg/100 mL (0.1 percent=1:1,000) for *Staphylococcus Aureus* to 1000 mg/100 mL (1 percent=1:100 for *Proteus vulgaris.* These concentrations are greatly in excess of the 1:20,000 concentrations of domiphen bromide found in commercial mouthwashes.

The minimum inhibitory concentrations (MIC's) of domiphen bromide within 48 hours, in the absence of organic material, ranged from 1:8,000 to 1:32,000 for gram-positive bacteria and from 1:125 to 1:2,000 for the gram-negative organisms. In the presence of blood the MIC's were 1:4,000 for gram-positive organisms and 1:32 to 1:500 for gram-negative organism. These MIC's are generally much in excess of the 1:20,000 domiphen bromide concentration found in commercial mouthwashes.

Kutscher et al. (Ref. 20) tested domiphen bromide against 18 pathogenic strains of *Candida albicans.* The concentration of domiphen bromide used was 0.01 percent. It was found that all of the test organisms were killed in 5 to 10 minutes. While this paper implies killing of *Candida albicans* by 0.01 percent (1:10,000) domiphen bromide in 5 to 10 minutes, critical examination of the methodology reveals that the investigators did not distinguish between fungicidial and fungistatic activity. Moreover, 0.01 percent domiphen bromide is twice the 0.005-percent concentration employed in commercial mouthwashes.

Knusel and Loustalot (Ref. 21) compared the effect of domiphen bromide and sodium fluoride on streptococci isolated from carious lesions in the rat and on microorganisms found in the saliva and mouths of the animals. The animals used were from a caries-prone strain. When domiphen bromide and sodium fluoride were administered in the drinking water, the concentration of domiphen bromide which produced a 50-percent inhibition of caries was 20 mg percent while 8.8 mg percent of sodium fluoride produced the same effect. In a separate experiment, domiphen bromide (3 mg percent) inhibited caries in 7 percent of the animals while a level of 30 mg percent inhibited caries in 54 percent of the test animals. A concentration of 10 mg percent sodium fluoride prevented caries in 50 percent of the animals. In addition to the cariostatic effects of domiphen bromide in situ, the authors studied the compound's ability to inhibit cariogenic streptococci and other similar microorganisms in vitro. Domiphen bromide inhibited reproduction of the bacterial strains at very low levels. For the streptococcus species, the MIC ranged from 0.5 to 5μg/mL; for *Staphylococcus aureus,* the MIC was 5 μg/mL; for lactobacillus species, the MIC was 50μg/mL. Sodium fluoride, in contrast, inhibited the reproduction of the experimental bacteria only a very high doses (MIC's ranged from 100 to 1,000 μg/mL). The authors stated that the potent effect of domiphen bromide on gram-positive cocci is noteworthy. They felt that the marked effect of domiphen bromide on bacterial reproduction recommended it as a caries inhibitor. During a discussion of their

results, they concluded that domiphen bromide had a strong caries-inhibiting effect, which was only slightly inferior to that of sodium fluoride. In contrast to sodium fluoride, domiphen bromide was effective against cariogenic streptococci and other types of microorganisms found in the oral cavity. In this study the 20 mg percent (1:5,000), 30 mg percent (1:3,750) required to produce approximately 50 percent inhibition of caries in the test animal was apparently administered ad lib to the animals in their water supply. Obviously, such quantities greatly exceed what a human would receive in a domiphen bromide mouthwash used a few times daily. The methodology and results of the in vitro studies are difficult to interpret.

Adair, Geftic, and Gelzer (Ref. 22) determined the minimum inhibitory concentrations of domiphen bromide and five other quaternary ammonium compounds against *Pseudomonas aeruginosa* ATCC 9027. Domiphen bromide had an MIC equal to 50 μg/mg while alkyldimethyl-benzylammonium chloride had a MIC of 100 μg/mL, alkyldimethyl 3,4-dichlorobenzylammonium chloride had MIC of 200 μg/mL. Cetyltrimethylammonium bromide, cetyldimethylethylammonium bromide, and cetylpyridinium chloride all had MIC's greater than 1,000 μg/mL. When resistance to alkyldimethylbenzylammonium chloride was developed in *Pseudomonas aeruginosa* ATCC 9027, the organism was also cross resistant to domiphen bromide and alkyldimethyl 3,4-dichlorobenzylammonium chloride. In this study the concentration of domiphen bromide utilized (50 μg/mL (1:20,000)) is equivalent to that contained in commercially available domiphen bromide mouthwashes. However, exposure time to this concentration was 10 days, a period of time which would not be achieved with a mouthwash.

None of the clinical studies supplied by a manufacturer as a Panel submission provide acceptable evidence for the effectiveness of domiphen bromide (Ref. 23).

Further studies by Wyler, Miller, and Micik (Ref. 24), Jaconia and Eisman (Ref. 25) and Weerts and Eisman (Ref. 26) did not use domiphen bromide as a single ingredient and therefore do not support the effectiveness of domiphen bromide.

Domiphen bromide manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of domiphen bromide as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older. Use a 0.005-percent concentration of domiphen bromide in the form of a rinse, mouthwash, or gargle not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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j. *Ethyl alcohol.* The Panel concludes that ethyl alcohol is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Chemically, ethyl alcohol is ethane with one hydrogen replaced by a hydroxyl group ($C_2H_5OH$) (Ref. 1). It is also known as hydroxyethane, ethanol, ethyl hydroxide, rectified spirit, spirits or wine, and by various other names. Pure alcohol contains not less than 92.3 to 93.8 percent by weight and 94.9 to 96 percent by volume of ethanol at 15.56° C, the remainder being water (Ref. 2). Alcohol has been made for many centuries by fermentation of various carbohydrates by yeast. Alcohol may also be produced synthetically by hydration of ethylene, which is available in abundance in natural gas and coke oven gases. Another synthetic method utilizes acetylene which is catalytically hydrated to acetaldehyde and then hydrogenated again, aided by a catalyst, to ethyl alcohol.

The term "proof spirit," as used in the United States, refers to a produce containing 50 percent by volume of alcohol. Fifty percent alcohol is sometimes designated as 100 proof. The strength of any solution of ethyl alcohol may be expressed in proof by multiplying the concentration of $C_2H_5OH$ by volume by two.

Alcohol is very hygroscopic, and concentrations above 95 percent must be made by special processing. The 95 percent alcohol boils at 78.2° C; the anhydrous alcohol boils at 78.3° C. It is not possible to obtain anhydrous alcohol (absolute alcohol) by direct distillation, since alcohol represents a constant boiling mixture of ethanol and water at 78.2° C. Absolute or "water-free" alcohol may be made by adding chemicals, such as anhydrous copper sulfate or calcium sulfate, which form hydrates and remove the water after which the alcohol is purified by distillation (Ref. 3).

Alcohol is a transparent, colorless, mobile, volatile liquid with a characteristic, somewhat pungent, odor and a burning taste. Alcohol is flammable. Alcohol is miscible with water in all proportions. It is also miscible with ether and chloroform. The specific gravity is not more than 0.816 at 15.56° C (Ref. 2).

The U.S. government has established regulations authorizing the addition of substances to alcohol which render it unfit for beverage purposes although suitable for industrial use. These various liquids are referred to as "denatured alcohols."

Diluted alcohol is a mixture of equal volumes of alcohol and purified water. This mixture contains between 41 and 42 percent by weight (48.4 to 49.5 percent by volume) of $C_2H_5OH$. When alcohol is mixed with water, a contraction in volume occurs. The specific gravity of diluted alcohol is between 0.935 and 0.937 at 15.5° C. Diluted alcohol is used mainly as a solvent for various pharmaceutical purposes. Concentrations up to 35 percent are used in certain mouthwashes. Higher concentrations cause burning of the mucous membranes. Rubbing alcohol consists of 68.5 to 71.5 percent by volume of absolute ethyl alcohol combined with a denaturant.

(1) *Safety.* The Panel concludes that ethyl alcohol is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

The safety of alcohol has been established through long-term use. Alcohol is a central nervous system depressant and produces coma analagous to other depressant drugs if overdosage occurs. Extensive studies indicate that there is a correlation between the concentration of alcohol in blood, urine, or expired air and the concentration on the nervous system. Alcohol is absorbed rapidly from the gastrointestinal tract when ingested in pure form or from alcoholic beverages. About 20 percent of orally ingested alcohol is absorbed by the stomach and the remainder by the intestines. The quantity absorbed from the mouth and throat is not significant. The rate of absorption is altered by the presence or absence of food in the stomach as well as the type of food present. Protein and fat delay absorption. The alcohol diffuses easily and rapidly into the tissues. The concentration in the tissues is related to the concentration of water present in the extracellular and intracellular compartments (Ref. 4).

From 90 to 98 percent of ingested alcohol is metabolized by oxidation in the liver. Acetaldehyde forms first, then acetic acid, and ultimately $CO_2$ and water (Ref. 5). Unmetabolized portions are excreted chiefly in the urine and to an insignificant degree in expired air. In expired air the concentration is approximately one two-thousandths of that of the arterial blood. In an obviously intoxicated person the urine may contain as much as 5 g/L; while at the same time the expired air contains only a few mg/L. Only traces are found in sweat, milk, and bile.

The effect of alcohol on the heart and circulation is not marked. Blood pressure and cardiac output may be slightly increased after ingestion of moderate amounts of alcohol. In moderate doses alcohol causes peripheral vasodilatation. A feeling of warmth and flushing of the skin is experienced. The vasodilation probably results from the central vasomotor depression (Ref. 4).

Alcohol has a marked influence on the gastric and intestinal digestion. Dilute alcohol solutions stimulate gastric secretions. Fifteen milliliters of 7 percent alcohol has been used as a test meal to promote secretion of hydrochloric acid. Accumulation of fat in the liver in normal individuals follows the ingestion of relatively small amounts of alcohol. This response to alcohol is acknowledged by some workers to be extremely valuable as a protective mechanism. Alcohol increases the rate of synthesis of fat by the liver slices. Apparently this is caused because of the increase of the ratio of reduced nicotinamide-adenine-dinucleotide ($NADH_2$) to non-reduced dinucleotide (NAD).

The local action of alcohol is mildly irritant, feeble, very slightly anesthetic, distinctly germicidal, and astringent. Alcohol has a marked potential for abuse, and for this reason the quantity used as a solvent in oral health care products is limited to 35 percent.

The symptoms of acute alcohol poisoning are widely known and a detailed description is unnecessary in a discussion of this type. However, it must be emphasized that there is a similarity between the symptoms of alcohol overdose and injuries and diseases that induce coma. Furthermore, alcohol acts additively with narcotics, hypnotics, and other central nervous system depressants that likewise cause coma.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of ethyl alcohol as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

Alcohol, in concentrations of less than 70 percent, is ineffective as an antimicrobial agent for use in medicine. Alcohol is widely used for application to the skin as an antimicrobial agent. Alcohol acts as an irritant, anhidrotic, and as an astringent by virtue of its ability to precipitate cellular protein. Thus, it is useful in the hygienic care of the skin in bedridden patients for the prevention of ulcers. Its cooling quality when it evaporates is well known. Alcohol may be used to remove phenol, poison ivy, etc. from the skin. Alcohol is a neurolytic agent and has been used for injection into nerves for relief of intractable pain. Alcohol has also been used to treat intractable pruritus. Intravenous alcohol has been reported to be effective as an anesthetic and basal narcotic, but the margin of safety is too narrow, and it is not used for this purpose. When taken internally, alcohol tends to increase sweating by dilating

the vessels of the skin. For this reason it is frequently used as a diaphoretic in mild infections, such as coryza. A 3-percent solution has been used for inhalation as an antifoaming agent in pulmonary edema.

Alcohol kills microorganisms by denaturing and precipitating proteins. It had been assumed that 95 percent ethyl alcohol is superior in its ability to kill bacteria on the skin. It is now well-established that 70 percent alcohol is more effective because 95 percent alcohol coagulates the cytoplasm on the periphery of the cell, and, therefore, is unable to penetrate into the cell. Most bacterial spores are resistant to alcohol (Ref. 6).

Concentrations that kill bacteria cause burining and intense discomfort and are too irritating when applied to ulcerations and inflammatory lesions on the mucuous membranes of the mouth and throat.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of alcohol as an antimicrobial agent for the treatment of symptons such as sore mouth and sore throat.

(3) *Proposed dosage.* The Panel recommends no dose for alcohol because it is used as a solvent for other active ingredients that possess antimicrobial activity and such combinations may act in consort with alcohol at doses below 70 percent of the effective antimicrobial dose.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B. 3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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k. *Eucalypto.*. The Panel concludes that eucalyptol is safe, but that there are insufficient data available to permit final classification of the effectiveness of eucalyptol as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Eucalyptus oil is a volatile oil obtained from the fresh leaves of *Eucalyptus globus.* It is also a constituent of that body of miscellaneous terpenes and other organic compounds obtained from plants referred to as the "volatile oils." Eucalyptus oil and its active ingredient eucalyptol have been described elsewhere in this document. (See part III. paragraph B.3.a. above—Eucalyptol, also part IV, paragraph A.9 above—Volatile oils.)

(1) *Safety.* The safety of eucalyptol has been described elsewhere in this document. (See part III. paragraph B.3.a.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of eucalyptol as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There are no data from controlled studies that establish eucalyptol or eucalyptus oil as an effective antimicrobial agent.

"The Merck Index" (Ref. 1) categorizes oil of eucalyptus as an expectorant, anthelmintic, and local anesthetic. Eucalyptol has been described in "United States Pharmacopeia" which states that it is used in dentistry as an antiseptic mouthwash. Eucalyptol is a mild irritant to the mucous membranes. Eucalyptol is considered a constituent of the volatile oils, and traditionally the volatile oils have been considered to have antimicrobial activity in the mouth and throat. The volatile oils have been discussed elsewhere in this document. (See part IV. paragraph A.9. above—Volatile oils.)

The Panel finds no data on eucalyptol's mode of action, spectrum of antimicrobial activity, conditions in which it acts topically, in vivo speed of antimicrobial activity, or under which conditions this occurs.

The Panel reviewed a submission in which a mixture of thymol, menthol, eucalyptol, and methyl salicylate was tested for antimicrobial activity (Ref. 2). It was allegedly found that eucalyptol possessed antimicrobial activity. The testing was not performed using the individual ingredient but by removing the eucalyptol from the mixture and determining the effectiveness of the mixture when eucalyptol was not present. The mixture, minus eucalyptol, exhibited less antimicrobial activity than when the eucalyptol was present. The Panel does not consider these data to be proof of the effectiveness of eucalyptol as an antimicrobial agent when used as a single ingredient.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of eucalyptol as and antimicrobial agent for treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.025-percent concentration of eucalyptol in the form of a rinse, mouthwash, or gargle not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervison of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 882–883, 1976.

(2) OTC Volume 130136.

1. *Gentian violet.* The Panel concludes that gentian violet is safe, but that there are insufficient data available to permit final classification of the effectiveness of gentian violet as an OTC antimicrobial active ingredient for topical use on the mucous membranes of

the mouth and throat when used within the proposed dosage limit set forth below.

Gentian violet is one of the triphenylamine (rosanaline) dyes which are derivatives of triphenylmethane. It is a mixture of several dyes, the most abundant of which is hexamethylpararosaniline chloride (Ref. 1). In addition, it contains pentamethylpararosaniline chloride and tetramethylpararosaniline chloride (Ref. 2). Chemically gentian violet must be considered a mixture of substances. Other related dyes are crystal violet and methyl violet. However, these are not absolutely identical to gentian violet, differing both in the specific methylrosaniline derivative present and in its proportions. Gentian violet is also known as aniline violet and crystal violet.

Gentian violet is a dark green powder, a crystallin mixture consisting of greenish pieces with a metallic luster, which is practically odorless. Gentian violet is soluble in water and chloroform and partially insoluble in ether. One gram dissolves in about 10 mL alcohol and approximately 15 mL glycerol (Ref. 2).

Synthetic organic dyes have been used for many years as antimicrobial agents, acting against bacteria, fungi, and protozoa. However, they have been supplanted by more effective and dependable antimicrobial agents and enjoy only limited use in treating infections. They have often been used for treating wounds. The antiseptic dyes have a marked specificity of action and each type of dye differs in its specificity. This specificity is dependent upon the staining properties of each type of bacteria. The staining properties of bacteria are largely dependent upon the physiochemical characterisitics of the constituents of the protoplasm of bacterial cells.

Antiseptic dyes fall into two groups, depending upon whether the chromogenic radical is electropositive or electronegative in the endoplasm and nucleus. The electropositive dyes have a special affinity for gram-positive organisms. They are also more active in a basic medium and, therefore, are called basic dyes. This does not mean that compounds themselves are basic, but rather that they have an affinity for chemically basic groups located in microbial cells. The acid dyes are active against gram-negative organisms and act best in an acid medium. Other factors such as species of organism, pH, concentration, and penetrability of the cell membrane also influence the activity of germicidal dyes. The antiseptic properties of dyes are greatly diminished in the presence of serum other other organic material Temperatures higher than that of the body also decrease their effectiveness.

The triphenylmethane or rosaniline dyes are basic dyes that have antiseptic properties and are effective against gram-positive organisms. The group includes, in addition to gentian violet, crystal violet, methyl violet, brilliant green, and acid and basic fuchsin. The first four are used medicinally.

Gentian violet and related dyes are particularly effective against staphylococcus. *Corynesbacterium diphtheriae,* and *Streptococcus pyogenes.* They are also effective against the causative organism of Vincent's angina, the various strains of candida, torula, epidermophyton, and trichophyton. Gram-negative bacteria are resistant to the rosaniline dyes. Rosaniline dyes form a precipitate with necrotic tissue. This property was once considered of unique value in the treatment of burns, but is not utilized in current therapeutics (Ref. 3).

The Panel reviewed one submission for a marketed product that contained labeling information but no data on the safety or effectiveness of gentian violet (Ref. 4).

(1) *Safety.* The Panel concludes that gentian violet is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Gentian violet is an antibacterial, antifungal, and anthelmintic dye. The oral $LD_{50}$ in mice and rats is 1.2 to 10 g/kg. Locally, when applied to the mucous membranes and skin, gentian violet is nontoxic. When ingested it may cause nausea, vomiting, diarrhea, and lassitude. Intravenous injection of impure preparations may produce a servere shock-like reaction.

Gentian violet has been used by the oral route as an anthelmintic because it is active against *Oxyuris vermicularis* (pinworm). Pinworm infection was once treated by giving 50 mg in enteric-coated tablets which had a 4-hour disintegration time, three times a day before meals for 8 to 10 days. Children were given 5 to 10 mg a day for each year of age in divided doses. After an interval of a week, the course was repeated.

Severe heart, kidney, or liver disease are considered to be contraindications to the use of the dye internally. Slough of the mucous membranes of the mouth has been reported in children when gentian violet was used as an anthelmintic dye.

(2) *Effectiveness.* The Panel concludes that there are insufficient data to permit the final clasification of the effectiveness of gentian violet as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed limits set forth below.

Gentian violet is bactericidal to gram-positive organisms, particularly staphylocci, *Corynebacterium diphtheriae,* and *Pseudomonas pyocyanea.* Gram-negative bacteria and tubercle bacilli are not affected by gentian violet. Gentian violet inhibits the growth of the spirochete that causes Vincent's angina as well as the growth of fungi such as candida, torula, epidermophyton, and trichophyton.

Gentian violet forms precipitates with necrotic tissue, and this property was formerly used in treatment of burns. Gentian violet is used in aqueous solutions to treat lesions of the skin and mucous membranes in which gram-positive bacteria are the causative pathogen. These lesions require identification by a physician and are not amenable to self-diagnosis and treatment.

Topical application of a 1-percent solution is effective in the treatment of infections due to *Candida albicans,* otherwise known as thrush. Diagnosis and treatment of thrush requires the services of a physician or dentist.

For the most part gentian violet has been replaced by more effective substances. It stains certain dental restorations and the oral tissues and is no longer used in the treatment of oral infections.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of gentian violet as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Swab affected area with a 1.0-percent solution of gentian violet not more than two to three times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist of physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral healt care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth

below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(2) "United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, p. 219, 1975.

(3) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol, et al., Mack Publishing Co., Easton, PA, p. 1091, 1975.

(4) OTC Volume 130051.

m. *Hydrogen peroxide.* The Panel concludes that hydrogen peroxide is safe, but that there are insufficient data available to permit final classification of the effectiveness of hydrogen peroxide as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Synonyms for hydrogen peroxide ($H_2O_2$) are hydrogen dioxide and hydroperoxide (Ref. 1). Hydrogen peroxide is a colorless, rather unstable liquid with a bitter taste, and it is caustic to the skin. It is miscible with water, soluble in ether, and insoluble in petroleum ether. Hydrogen peroxide is decomposed by many organic solvents. Solutions of hydrogen peroxide gradually deteriorate and are usually stabilized by the addition of acetanilide or similar organic materials (Ref. 1).

Hydrogen peroxide solution 3 percent, also known as hydrogen dioxide solution or oxydol, contains 2.5 to 3.5 percent by weight of $H_2O_2$ which is equal to 8 to 12 volumes of oxygen. It is classified as a topical anti-infective (Ref. 1). This concentration has been widely used as a cleansing and topical antiseptic agent for suppurative wounds and inflammation of the skin and the mucous membranes. The dental profession also uses it for irrigation during root canal therapy and as a mouth rinse for acute necrotizing gingivitis. The unpleasant taste of hydrogen peroxide has been suggested to be due to the acetanilide (Ref. 2).

The 30-percent solution of hydrogen peroxide (superoxol) is a strong oxidizing agent that has been used for bleaching of vital and pulpless teeth. The soft tissues of the mouth should be protected against its irritant action by the use of a rubber dam.

The decomposition of hydrogen peroxide can be hastened by the action of enzymes, such as catalase (hydrogen peroxide oxidoreductase), peroxidases, reduced nicotinamide adenine dinucleotide phosphate (NADP), and cytochrome c.

In the decomposition of hydrogen peroxide, one molecule releases one atom of oxygen which combines with a substrate that is oxidized.

(1) *Safety.* The Panel concudes that hydrogen peroxide is safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

A submission to the Panel on hydrogen peroxide contains no data relating to any aspect of safety (Ref. 3). However, a submission to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Ref. 4) contains a literature review as well as studies with 10 percent hydrogen peroxide contained in proprietary gels.

The comparative oral irritant actions of hydrogen peroxide and sodium perborate, when these substances were used as dentifrices, have been described (Ref. 5). Sodium perborate was found to be the more irritating, although hydrogen peroxide also produced noticeable changes,such as edema and ulceration of the mucous membranes of the gingival and lingual areas. Hydrogen peroxide should not be used as a mouthwash for long periods of time. The acidity of even diluted solutions of hydrogen peroxide will result in the decalcification of tooth substance. Continued long use may also result in the development of a black hairy tongue (Ref. 6).

Relatively little information has been found in the literature regarding the acute toxicity of hydrogen peroxide, but it appears to be low. Spector (Ref. 7) states that the approximate $LD_{50}$ for rats is 21 mg/kg if given intravenously and 700 mg/kg when applied cutaneously. Gosselin et al. (Ref. 8) also indicate a low toxicity. They comment that there are no primary effects when hydrogen peroxide is ingested because it is decomposed in the bowel before absorption. However, decomposition is associated with the release of large volumes of oxygen, a volume of oxygen equal to 10 times the volume of the solution, and esophagitis and gastritis may occur. Rupture of the colon, proctitis, and ulcerative colitis have been reported to follow hydrogen peroxide enemas.

There are studies (Ref. 4) that estimate that the $LD_{50}$ of 10 percent hydrogen peroxide contained in various gels that were adminstered orally in six rats is over 5 g/kg. No controls were used, so the possible inactivation of peroxide toxicity by the gels is uncertain. No irritation of the stomach mucosa was observed in the rats receiving 10 percent hydrogen peroxide in gels, although only 2 rats were sacrificed. The same studies indicated that 0.2 mL of the test gels were only transiently irritating in hamster cheek pouches in 24 animals or guinea pig gingiva in 6 animals.

Martin et al. (Ref. 9) studied the irritant effect of hydrogen peroxide on the gingiva of anesthetized dogs by applying a 1-percent solution via a continuous drip onto a cotton pledget at the rate of 15 mL/hr. The number of animals used was not stated. Edema resulted which was followed by complete destruction and sloughing of the cornified layer of the epithelial cells. Other histological changes were also noted.

In a similar study, Dorman and Bishop (Ref. 10) applied 1.2 percent hydrogen peroxide by continuous drip to tongues of 10 anesthetized dogs. Edema invariably occurred within 30 minutes, reaching a peak in 3 to 4 hours.

In a study of the possible anticariogenic effects of 0.5 percent to 1.5 percent hydrogen peroxide added to the drinking water of rats, Shapiro, Brat, and Ershoff (Ref. 11) noted that growth, as determined by body weight, was retarded over an 8-week period as compared to the controls. However, the control animals were neither pair-fed nor pair-watered so this observation is not conclusive. Lisanti and Eichel (Ref. 12) also noted a weight reduction in hamsters receiving 3 percent hydrogen peroxide in the drinking water for 55 days, but there again pair-feeding and pair-watering were not done.

Eighty-eight dental students self-administered a 6- to 12.5-percent hydrogen peroxide solution (Ref. 4). They used it as a mouthwash or dipped their toothbrushes into the solution before brushing their teeth. Application of the hydrogen peroxide was 2 to 3 times per day for a period ranging from 1 to 2.5 months. Some gingival changes were noted (6.4 percent "redder," 3.4 percent "paler") and 6.8 percent of the group developed hyperkeratinized filiform papillae of the tongue. Black hairy tongue, which seems to be associated mainly with prolonged usage of carbamide peroxide and sodium perborate (Ref. 13), was not observed.

Biopsies of the attached interdental epithelium of 30 male patients were made after topical application with 30 percent hydrogen peroxide (Ref. 14). The peroxide was applied three times per week for 4 weeks to the interdental papilla. Applications were for 1 minute, followed by irrigation with water. The mitotic index was increased 5 to 8 fold.

However, single applications of hydrogen peroxide has the effect of a prolongation of mitosis suggesting that the increased rate of mitosis was more apparent than real.

In a study by Orban (Ref. 15), the application of 30 percent hydrogen peroxide twice weekly for 3 to 6 weeks was reported to result in significant changes in the epithelium and connective tissues of chronically inflamed gingival tissue. The basal cell layer became considerably thicker, an increase in mitosis was noticed, and irregular rete pegs penetrated deeply into the connective tissue. Proliferation of the connective tissue took place, and hyperkeratosis of the epithelium was observed. The author interpreted these changes as beneficial for healing. No mention was made of the number or age of the subjects used, the exact site of application of the agent (although application to the free gingiva is shown in a photograph), the method of application, or the duration of application.

One reference, without referring to any experimental data, stated "hypochlorite or peroxide solutions at concentrations above 7 percent may be regarded as toxic to soft tissue, and hence must be used prudently" (Ref. 16).

Knighton (Ref. 17), however, states that hydrogen peroxide should not be used on newly granulating surfaces because it tends to break down the new, delicate tissue growth.

The Panel concludes that concentrations up to 3 percent of hydrogen peroxide are safe for OTC use on the mucous membranes of the mouth and throat.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of hydrogen peroxide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Most bacteria are relatively resistant to the action of peroxides. This relative resistance may be the result, in part, of the bacterial production of the enzyme catalase that is present in some cytochrome-containing aerobic and facultative anaerobic bacteria. Some anaerobic bacteria that lacks catalase produce peroxidase enzymes in lieu of the catalase. Both catalases and peroxidases are listed under the general enzyme classification "hydroperoxidases."

Hydrogen peroxide, if allowed to reach a high concentration, is toxic to bacteria in vitro. However, the concentration of the "hydroperoxidases" either by the bacteria themselves or by the tissues in vivo prevents the accumulation of this large threshold concentration.

Catalase has two activities. It decomposes hydrogen peroxide, and it oxidizes secondary substrates. Catalase activity is present in nearly all human organs and cells. The liver and kidney and the erythrocytes are rich in catalases. Oral tissues also have tissue catalases. The tissue catalases function in the same manner as microbial catalases, i.e., they prevent the accumulation of noxious $H_2O_2$.

Human leukocytes and erythrocytes produce peroxidases. The saliva contains salivary peroxidases. The mechanism of action of these peroxidases is similar to the action of the catalases. The released oxygen combines with a substrate to form another compound and no gas is evolved.

One molecule of catalase can deompose 44,000 molecules of hydrogen peroxide per second. This indicates that a minute amount of enzyme is able to decompose a large amount of peroxide.

It was long thought that the activity and growth of obligate anaerobes were inhibited or killed by hydrogen peroxide because they lack the catalase possessed by some aerobes, e.g., *Staphylococcus aureus.* However, aerobes and facultative anaerobes, which lack catalase, are not necessary killed by $H_2O_2$. Recent findings suggest that a highly reactive and very toxic superoxide formed by flavoenzymes inhibits anaerobes because they do not produce the superoxide dimutase produced by aerobes.

Alternatively, the maintenance of certain essential enzymes in an oxidized state may prevent some anaerobes from multiplying because oxygen prevents flavoproteins from functioning (Ref. 18). The potential activity of $H_2O_2$ is, therefore, complex and requires a knowledge of the metabolic pathways of the specific susceptible or resistant microorganisms.

In one clinical study (Ref. 19), 0.3 percent hydrogen peroxide was compared with 0.3 percent sodium peroxyborate in reducing the severity of acute necrotizing ulcerative gingivitis. Twenty-five patients were used in each group during a double-blind trial. As judged by clinical observation and patient response, both compounds were found to be effective with no statistically significant differences between the two compounds. However, since this study utilized no control, the efficacy could have been due to a mechanical effect which might be obtained by rinsing with saline solution or water.

Another study, although not designed to directly evaluate the clinical effectiveness of hydrogen peroxide, contains data which should be noted. In this study, which was designed to evaluate antiseptic activity, six subjects rinsed their mouths for 1 minute twice daily over a 5-day period with 0.5 percent hydrogen peroxide suspended in 33 percent glycerin. No irritation of the oral mucosa was noted, but when 0.75 percent hydrogen peroxide in 50 percent glycerin was used "certain subjects noted irritation of the mouth and gums as evidenced by chapping and loss of taste." No explanation for this observation is offered, but it seems probable that these effects could have been due to the humectant effect of the 50-percent glycerin rather than the 0.75-percent hydrogen peroxide (Ref. 20).

A further reference suggests that hydrogen peroxide "is one of the better agents" to discourage new tissue proliferation and promote epithelialization over the newly formed tissue (Ref. 16). The application, which is not described, was intended to be used after periodontal surgery. No substantiating data are presented.

Many bacteriological studies have been performed with more stable forms of hydrogen peroxide, such as carbamide peroxide in glycerin, but relatively few with hydrogen peroxide alone. Concentrations as low as 0.1 to 0.25 percent are said to kill *Escherichia coli* and *Staphylococcus aureus* in 1 hour, but in 5 minutes. Obviously, the 1-hour in vitro exposure time is unlikely to occur in vivo because of the rapid decomposition by tissue and salivary catalase and by tissue peroxidase. In fact, most of the early reports, circa 1940 to 1950, on the bacterial activity of hydrogen peroxide in vitro failed to take into account the conditions which exist in vivo and include rapid breakdown in the presence of tissue, blood, and saliva. It is difficult to imagine circumstances whereby hydrogen peroxide kills bacteria, but is not injurious to tissue.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of hydrogen peroxide as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use hydrogen peroxide in concentrations up to 3 percent. For children under 3 years of age, there is no recommended dosage except the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial

active ingredients. (See part IV. paragraph B.2. above—Categroy I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co.; Rahway, NJ, p. 633, 1976.

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(3) OTV Volume 130060.

(4) OTC Volume 080050.

(5) Dobbs, E. C., "Pharmacology and Oral Therapeutics," 12th Ed., C. V. Mosby Co., St. Louis, p. 427, 1961.

(6) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 314, 1977.

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n. *Iodine.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of iodine as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Iodine is an element, being one of the four halogens. All four halogens are oxidizing agents. Its moleculer is diatomic ($I_2$). It was first discovered in 1811 by Courtois (Ref. 1). Iodine is obtained from seaweed and certain algae, in sea water, brine, oil field brines, and from Chilean saltpeter. Elemental iodine consists of bluish-black scales or plates with a metallic luster (Ref. 2). It sublimes, giving off a violet vapor which is corrosive. Iodine melts at 113° C, but is volatile at ordinary room temperature. One gram dissolves in 2,950 mL water, 12.5 mL alcohol, 10 mL benzene, 50 mL carbon tetrachloride, and 80 mL glycerin. It is freely soluble in solutions of water-soluble iodides, such as those of sodium and potassium, and in mixtures of alcohols and aqueous iodides. These hydroalcoholic solutions are used as germicides and belong to a group of iodinated compounds called "iodophors."

Iodine is incompatible with oil of turpentine, starch, tannin, alkalis, alkaloids, and metallic salts.

Iodine is an essential element found in plant foods. Animals used for food that feed on plants containing iodine are also a source of the element. Iodine deficiency results in goiter. The minimal daily requirement of iodine has been estimated to be 100 μg in terms of elemental iodine. Iodine was first used therapeutically in 1819 for the treatment of goiter. Iodine preparations have been listed in the "United States Pharmacopeia" since 1840.

The acceptable composition for tincture of iodine is not less than 1.8 g and not more than 2.2 g of iodine, and not less than 2.1 g and not more than 2.6 g of sodium iodide in each 100 mL of 44 to 50 percent ethyl alcohol or an appropriate denatured alcohol.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of iodine as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Elemental iodine has local irritant and germicidal actions (Ref. 1). It has been used as a counterirritant in various forms of arthritis, particularly those due to trauma. Solutions of elemental iodine have been a frequent cause of poisioning. The symptoms of acute toxic reactions are pain in the epigastrium followed by nausea and vomiting. The vomitus may be brown or blue if there has been any starch in the stomach and later may become bloody. Excessive thirst, abdominal cramps, and circulatory failure may follow in severe cases. The most efficient antidote is a solution of sodium thiosulfate. When this is not available, several tablespoonsful of cornstarch stirred with water may be used. In its absence, bread or other starchy materials may be ingested (Ref. 3).

Iodine or iodine derivatives, such as sodium or potassium iodine, and organic compounds containing iodine which are given continuously over long periods of time, even in medicinal doses, give rise to a more or less serious type of chronic toxicity known as iodism. This is usually characterized by pain or heaviness in the region of the frontal sinuses. In some instances, soreness of the mucous membrane of the mouth and throat results. Skin lesions of all degrees of severity have followed internal use of iodides in sensitive persons. Absorption of iodides has caused the shrinkage of the breasts in the famale and atrophy of the testicles in the male. The protracted use of iodides may cause parotitis apparently due to plugging of the ducts of the salivary glands by dead or injured cells. In some instances, sensitivity to iodides may be responsible for vasculitis and polyarteritis.

Gleason et al. (Ref. 4) rate the toxicity of elemental iodine as 5 (extremely toxic, with a probable lethal dose of 5 to 50 mg/kg). A study of attempted suicides associated with iodine ingestion indicates that the lethal range is from a few tenths of a gram to more than 20 g (Ref. 5). The probable mean lethal dose is between 2 and 4 g of free elemental iodine. Poisoning is mainly due to its oxidizing and the corrosive action on the gastrointestinal tract. Povidone-iodine is less toxic than the iodine and other iodophors.

Iodine produces a mahogany stain when applied to the skin. Smarting, erythematous inflammation, infiltration of subcutaneous tissue, desquamation of the epidermis into large shreds, and vesication of tissues may result after repeated application.

The effects of iodine on the mucous membranes are even more severe than on the skin and may produce ulceration, corrosion, and sloughing. This action is chemical in nature since it precipitates protein. The protein dissociates the releases iodide so that its action is prolonged, as it is in skin. Iodine is absorbed, somewhat, from the skin and excreted mainly in the urine as the iodide ion. Dilute solutions in non-irritating strength are absorbed from the mucous membranes and are distributed systemically. (See part IV. paragraph B.3.t. below—Povidone-iodine.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of iodine as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Elemental iodine is one of the most potent germicides available. However, its effectiveness as an antimicrobial agent on the mucous membranes of the mouth and throat in the relief of the symptoms of sore throat and sore mouth has not been established.

Iodine has a long history of use as a broad-spectrum antimicrobial agent. It is recognized as having activity against fungi, viruses, and both gram-positive and gram-negative bacteria. The phenol coefficient of iodine may vary between 180 and 237 depending upon the character of the solvent and the species of bacteria tested. It is believed that all microrganisms are killed by the same concentration of iodine, but that various environmental conditions in a wound or on the skin or other surfaces cause changes in the concentration necessary for the killing effect. Albumin decreases the bactericidal action of iodine. In the presence of blood serum a 1:200,000 solution has been bactericidal to staphylococci. Most antiseptics are ineffective aganist tubercle bacilli, but iodine in concentrations as low as 0.0625 percent is bactericidal to human tubercle bacilli in cultures and suspensions. Iodine will kill anthrax spores, but solutions as strong as 7 percent of the tincture must be used, and an exposure of 2 hours is required for such an action.

Iodine is still considered by many to be one of the best wound disinfectants, but it should never be applied in concentrations greater than 2 or 3 percent. Iodine has been and, in some cases, is still used to sterilize the skin prior to surgical procedures. It may be employed in strengths of 5 to 10 percent for this purpose. Iodine is of benefit in the treatment of fungus infections of the skin such as ringworm, foveas, etc. In these conditions, it may be applied as a solution of the tincture (Ref. 6).

Elemental iodine precipitates proteins. The iodine is partly absorbed, partly loosely bound, and partly converted into iodide ions. This precipitation causes persistent irritation, usually short of corrosion. Since the iodine itself is loosely bound, it continues to penetrate into the cells so that the action extends deeply. In the process of acting as an antimicrobial agent, iodine also injures some of the host cells. The effect of this type of injury on wound healing is a matter of concern to the Panel. The iodine is used in the form of tinctures or watery (hydroalcoholic) solutions.

The official tincture contains 3.5 percent iodine and a "strong solution" (Lugol's solution) contains 7 percent iodine in potassium iodide. The potassium iodide makes the tinctures more stable and more miscible with water. Iodine ointments release their iodine slowly so their action is milder and less effective than that of solutions. A part of the iodine is chemically combined with the base in some of the proprietary ointments so that it cannot react with the proteins and is, therefore, ineffective.

The antiseptic action of iodine is used to prepare the skin for operations. A 3-percent alcoholic solution is painted over the dried skin in the operative field on the preceding day and again on the day of the operation. This is preferable to the official tincture since the potassium iodide in the latter delays drying and penetration. Severe irritation may result. The value of iodine for wound disinfection is disputable on the basis that the tissue injury may be more of a detriment and delay wound healing, offsetting the benefits of its antiseptic action. Extensive application to the skin sometimes produces nervous phenomena and fever.

These effects of iodine on the skin and minor wounds are mentioned in detail to emphasize the potency of iodine as an antimicrobial agent and to indicate that it is capable of causing injury to the host cells. The cells of the mucous membranes of the oral cavity are more delicate and are more easily injured by chemical agents than those of the skin. The Panel is concerned about the possible adverse effects of iodine in the mouth and throat. Insufficient data exist concerning such adverse effects particularly for use in rinses and mouthwashes on a daily basis for months at a time.

Iodine manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of iodine as an antimicrobial agent for the treatment of symptoms such as sore throat and sore mouth.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 1.0- to 2.0-percent concentration of iodine in aqueous-alcoholic solutions in the form of a rinse, gargle, spray, or swabbed over the affected area, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Date Required for Evaluation.)

**References**

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, "8th Ed., W. B. Saunders Co., Philadelphia, pp. 1117–1120, 1957.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 661–662, 1976.

(3) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 886–887, 1977.

(4) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, section II, p. 82, and section III, pp. 126–128, 1969.

(5) Moore, M., "The Ingestion of Iodine as a Method of Attempted Suicide," *New England Journal of Medicine,* 219:383–388, 1938.

(6) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 625–628, 1973.

o. *Menthol.* The Panel concludes that menthol is safe, but that there are insufficient data available to permit final classification of the effectiveness of menthol as an OTC antimicrobial agent for topical use on the mucous

membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Menthol is also known as hexahydrothymol and peppermint camphor (Ref. 1). It is a secondary alcohol obtained from peppermint oil and other mint oils or prepared synthetically by hydrogenation of thymol. Menthol is used as an analgesic, antipruritic, and local stimulant to the mucous membranes and as a counterirritant. The general characteristics of menthol have been described elsewhere in this document. (See part III. paragraph B.1.f. above—Menthol).

(1) *Safety.* The safety of menthol has been described elsewhere in this document. (See part III. paragraph B.1.f. (1) above—Safety).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of menthol as an OTC active antimicrobial ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Menthol is a constituent of certain volatile oils, depending upon the source of the oil. Menthol is lipophilic and, for this reason, has been regarded as an antimicrobial agent. It is actively germicidal, being more powerful than phenol (Ref. 2). Gershenfeld and Miller (Ref. 3) found that even the saturated aqueous solution, which is very dilute, has some antiseptic properties; however, there are no data to indicate the broadness of its spectrum and the degree of its antimicrobial activity. Menthol has been administered orally in the doses of 30 to 120 mg as an interal antiseptic. Menthol is used topically in a 1- to 10-percent solution. Diluted solutions have been used to control superficial infections on the skin.

A submission, in which a mixture of thymol, menthol, eucalyptol, and methyl salicylate was tested in vitro for antimicrobial activity, alleges that menthol possesses antimicrobial activity (Ref. 4). The testing was not performed with the individual ingredient alone. The testing was performed by removing menthol from the mixture and determining the effectiveness of the mixture when menthol was absent. Less antimicrobial activity was noted when the menthol was removed. The Panel does not consider this data to be proof of effectiveness of menthol as an antimicrobial agent when used as a single ingredient.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of menthol as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.04- to 2.0-percent concentration of menthol in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 2.0 to 20.0 mg of menthol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 757, 1976.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 697, 1973.

(3) Gershenfeld, L., R. E. Miller, "The Bactericidal Efficiency of Menthol and Camphor," *American Journal of Pharmacy*, 105:490–500, 1933.

(4) OTC Volume 130136.

p. *Methyl salicylate.* The Panel concludes that methyl salicylate is safe, but that there are insufficient data available to permit final classification of the effectiveness of methyl salicylate as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has evaluated methyl salicylate as a topical anesthetic/analgesic elsewhere in this document. (See part III. paragraph B.3.b. above—Methyl salicylate.)

(1) *Safety.* The safety of methyl salicylate has been described elsewhere in this document. (See part III. paragraph B.3.b.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of methyl salicylate as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There are no data from controlled studies that establish methyl salicylate as an effective antimicrobial agent. Methyl salicylate is used topically on the skin as a rubefacient and counterirritant. None of the references reviewed by the Panel indicate that the individual ingredient is or has been used as an antimicrobial active ingredient in the mouth and throat (Refs. 1 through 6). A submission to the Panel presented data in support of the antimicrobial activity of methyl salicylate (Ref. 7). These data merely indicate that when methyl salicylate is removed from the tested formulation, which contained other ingredients, bacteriostatic and bactericidal activity was reduced. Data on the antimicrobial activity of the ingredient alone was not presented. The Panel does not consider a study of this type supportive of claims that methyl salicylate is an effective antimicrobial agent.

The Panel concludes that there are insufficient data to establish the effectiveness of methyl salicyclate as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use up to a 0.4-percent concentration of methyl salicylate in the form of a rinse, mouthwash, gargle, or spray, not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) OTC Volume 130042.
(2) OTC Volume 130043.
(3) OTC Volume 130044.
(4) OTC Volume 130045.
(5) OTC Volume 130046.
(6) OTC Volume 130047.
(7) OTC Volume 130136.

q. *Oxyquinoline sulfate (8-hydroxyquinoline).* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of oxyquinoline sulfate as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Oxyquinoline sulfate is a salt made by reacting oxyquinoline with sulfuric acid.

Oxyquinoline has also been called oxine, 8-hydroxyquinoline, oxybenzopyridine, phenopyridine, 8 quinolinol, and oxychinolin (Ref. 1). The quinolines (n-quinoline and isoquinoline) are derived from naphthalene by substituting a trivalent notrogen atom for a carbon atom in one of the aromatic rings, converting the compound into a tertiary amine. The compound then possesses basic properties and reacts with acids to form salts. A hydroxyl group substituted on position 8 of the aromatic nucleus of quinoline converts it to oxyquinoline and confers phenolic properties. Oxyquinoline, therefore, is both a phenol and an amine and manifiests either acidic or basic properties depending upon the acidity or alkalinity of the solvent in which it is incorporated. Oxyquinoline is manufactured by heating *o*-aminophenol with *o*-nitrophenol, glycerol, and sulfuric acid ($H_2SO_4$) (Ref. 1).

Oxyquinoline base is a white crystalline powder that is almost insoluble in water and ether, but freely soluble in alcohol, acetone, chloroform, and benzene. It is also soluble in aqueous mineral acids and in glycerol (Ref. 1). Oxyquiniline melts at 76° C and boils at approximately 267° C. Oxzyquinoline is used in industry as a chelating agent to precipitate metals. Oxyquinoline is known in industry as 8-HQ. It is not used in its basic form for medicinal purposes due to its poor water solubility. Oxyquinoline is, however, used in the form of one of its water-solube salts, among which are the sulfate, citrate, tartrate, and benzoate. The most commonly used salt is oxyquinoline sulfate. Oxyquinoline sulfate is a yellow crystalline powder with a slight saffron odor and a burning taste. It melt between 175 and 178° C. It is freely soluble in water; soluble in approximately 1 part in 100 parts of glycerine; slightly soluble in alcohol; and insoluble in ether. The sulfate has been used as a bacteriostatic agent in the treatment of athletes' foot, vaginitis, and as a gargle, eyewash, and in hemorrhoidal preparations (Ref. 2). Oxyquinoline sulfate has been classified as a bactericide, fungicide (especially against candida), and a tichomonacide (Ref. 3).

Oxyquinoline benzoate is a slightly yellow crystalline substance, soluble in water, slightly soluble in alochol, and nearly insoluble in ether and alkaline aqueous sulutions (Ref. 2). It has been used for the same purposes as oxyquinoline sulfate. Oxyquinoline citrate is also a yellow crystalline powder with a saffron-like odor. It is freely soluble in water. Solutions are acid in reaction (Ref. 2).

Various iodinated and chlorinated quinoline derivatives have been or are still in use as amebicides. Among these are iodohydroxyquinoline sulfuric acid, iodochlorohydroxyquinoline, and diiodohydroxyquinoline. They are effective against amebae on the surface of the intestinal mucosa. The parasites in the submucosal tissues are unaffected. They most likely exert their antimicroboal effects by inactivating the enxymes or halogenating the proteins of the amebae.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of oxyquinoline as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Quinoline itself has been suspect for many years. In a study performed in 1881, quinoline (oxyquinoline minus the hydroxyl group) was found to be strongly antiseptic and toxic (Ref.4). It is possible that the presence of hydroxyl group diminishes its toxicity. The administration of 0.2 g/kg subcutaneously and intravenously produced retinitis (Ref. 4). The lesions noted were similar to those produced by naphthalene. Some of the more recently introduced iodo-, chloro-, or iodo- and chloro-substituted quinolines used to threat amebiasis have been found to cause optic nerve atrophy.

The acute toxicity of oxyquinoline sulfate, on the other hand, appears to be low. Gleason (Ref. 5) states that rabbits can tolerate single oral doses of 3.7 g/kg of the sulfate when mixed with posassium sulfate. Rats, guinea pigs, and dogs tolerate large quantities after oral administration. The acute $LD_{50}$ in guinea pigs is 175 g/kg. The $LD_{50}$ in rats is 32 g/kg after 1 week. In dogs there was no mortality. Animal and human data on chronic toxicity are not available. Long-term clinical use of oxyquinoline salts appears to indicate that these derivatives have a low degree of toxicity.

The fate of oxyquinoline in the body was first studied in 1899 and later in 1928 (Ref. 4). It is rapidly absorbed from the intestines of dogs and rapidly excreted into the urine conjugated with sulfuric acid as "ethereal sulfate." Conjugation occurs at the phenolic hydroxyl group. A small part is excreted unmetabolized in the urine and some in the bile. Its metabolic fate in man has not been reported.

Besides the salts of oxyquinoline, monoiodinated derivatives such as iodochlorhydroxyquin and diiodinated derivatives have been used as amebicides.

Skin sensitivity and severe irritation have been reported in workmen during industrial use. Irritation and sensitization have also been reported after repeated application of the salts of oxyquinoline incorporated for topical use on the skin.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of oxyquinoline sulfate as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Oxyquinoline sulfate is considered to be primarily bacteriostatic, since it is feebly bactericidal. Its exact mode of action has not been established, but it is believed to act by chelating various metals required by microorganisms for metabolism. Among these are iron, cobalt, copper, and magnesium. Other drugs believed to act in a like manner are salicylates, thiourea, thiouracil, the tetracyclines, cortisone, and penicillin. Oxyquinoline sulfate is presumed to form a copper chelate which easily passes into the cell of an invading pathogen. After the chelate enters the cell it undergoes a chemical change that releases copper which, in turn, kills the organism. Thus, the drug acts by allowing the passage of small amounts of copper chelated from the host's tissues into the invading organism (Ref. 5). It has also been suggested that it may act on the cell membrane and alter its stability and permeability. The amount chelated from the host is not sufficient to cause harm, but is sufficient to adversely effect the microorganisms.

The antimicrobial activity of oxyquinoline in vitro is subject to many influences, such as concentration, temperature, and pH, all of which make its action difficult to predict. It is the consensus of the Panel that if its action in vitro, where variables can be eliminated, is unpredictable, then its in vivo behavioir is less predictable.

Oxyquinoline sulfate has been used in a 1:1,000 solution externally on the skin, in a 1:3,000 aqueous solution as a nasal spray and as an eyewash, in a 1:2,000 aqueous dilution as a gargle, and in a 1:1,000 dilution as a vaginal douche. In dentistry, it is used as an oral antiseptic. A 1- to 2-percent solution is used to treat pus cavities either as an irrigant or soaked in a gauze pack. Oxyquinoline sulfate has also been used internally as an antimicrobial agent for dysentery. Oxyquinoline salts are said to be effective against candida and trichomonas.

Oxyquinoline sulfate manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel does not have data from controlled studies on oxyquinoline sulfate's effectiveness as a broad-spectrum antimicrobial agent. Since controlled in vivo studies are not available, the Panel cannot make a judgment concerning the effectiveness of oxyquinoline sulfate as an antimicrobial agent for the treatment of symptoms of sore mouth and sore throat (Ref. 6).

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.1-percent concentration of oxyquinoline sulfate in aqueous solution in the form of a rinse, gargle, or spray not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 644, 1976.

(2) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1103, 1975.

(3) DerMarderosian, A. H., "Pesticides," *in* "Remington's Pharmaceutical Sciences," 14th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA. p. 1194, 1970.

(4) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., p. 824, 1957.

(5) Crossland, J., "Lewis's Pharmacology," 4th Ed., E. and S. Livingstone, London, pp. 1124–1125, 1970.

(6) "The Merck Index," 5th Ed., Merck and Co., Rahway, NJ, p. 279, 1940.

r. *Phenol.* The Panel concludes that phenol is safe, but that there are insufficient data available to permit final classification of the effectiveness of phenol as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has classified phenol as a Category I anesthetic/analgesic and has described its general characteristics elsewhere in this document. (See part III. paragraph B.1.g. above—Phenol.)

(1) *Safety.* The Panel concludes that phenol is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has described the safety of phenol elsewhere in this document. (See Part III. paragraph B.1.g.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of phenol as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenol was the first antimicrobial agent to be used in medicine. Lister first used it in 1967 as a sterilizing agent for surgical instruments and as an antiseptic (Ref. 1). In high concentrations phenol is a protein precipitant; at lower concentrations it is a protein denaturant. Phenol exerts an antimicrobial action by denaturing the protein of living cells. An easily dissociated complex of phenol and the protein is formed. This ability to form a comlex permits the penetration of phenol through the intact or abraded skin, subcutaneous tissues, and mucous membranes with which it comes into contact (Ref. 2).

As is the case with most antimicrobial agents, phenol is not effective against all types of microorganisms. In appropriate strengths (0.5 to 1.5 percent) aqueous solutions of phenol rapidly destroy nearly all forms of bacteria. However, phenol is generally not sporicidal. Anthrax spores may not be killed even after 24 hours exposure to a 5-percent aqueous solution of phenol (Ref. 1). A 1-percent solution destroys nonsporulating organisms after a sufficiently prolonged exposure. A 2-percent solution does so more promptly.

Aqueous solutions of phenol in a proportion of 1:800 are bacteriostatic and inhibit the multiplication of bacteria. Its value as a germicide is due largely to the fact that its activity is only slightly diminished in the presence of proteins. Concentrations of phenol exceeding 1:5 percent also denature the proteins of cells of healthy tissues. For this reason phenol has been supplanted by other antimicrobial agents (Ref. 3).

Phenol has been widely adopted as a standard for comparison of the disinfectant power of antimicrobial agents. According to Harvey (Ref. 2), the concept of using it as a means of comparison of bactericidal power of antimicrobials was originally suggested by Walker and Rideal in 1903. The standard is termed the "phenol coefficient." An antimicrobial agent with a microbial activity equal to that of phenol would have a coefficient of 1.0. An antimicrobial agent killing twice the number of microbes of a particular strain under standard and identical conditions would have a phenol coefficient of 2.0. Some antimicrobial agents when tested against certain organisms have coefficients of over 1,000. For this reason other microbial agents have supplanted phenol as an antiseptic.

The nature of the medium in which phenol is dispersed or dissolved greatly influences its germicidal activity. Generally, aiqueous solutions are the most effective preparations. Phenol has a high oil/water partition coefficient and is slowly released from a lipid phase. Phenol is therefore practically ineffective in fats and animal and vegetable oils when applied topically. In addition, its antibacterial effect is greatly reduced when incorporated in petrolatum. Alcohol and glycerin both diminish its germicidal action while sodium chloride allegedly enhances it. The bactericidal effectiveness of phenol is greatly reduced at low temperatures and in an alkaline medium (Ref. 1).

Phenol is relatively ineffective as an antimicrobial agent when incorporated in soaps. Phenol was once widely used as a disinfectant, for sanitation, and as a germicide for various medical and surgical purposes, but it has been replaced largely by more effective, less toxic compounds. Phenol is fungicidal in concentrations of 1.3 percent or more (Ref. 3).

Even though phenol precipitates and denatures protein, its antibacterial activity continues in the presence of protein because it subsequently

separates from the combination and continues to penetrate into a protein mass, such as sputum, mucus, and other organic materials. Camphor added to phenol in liquid petrolatum greatly reduces the local action and absorption of phenol. Apparently the camphor "holds" the phenol by acting as a solvent or forming a complex. Moisture favors the release of the phenol from the complex. A combination containing 4 percent phenol, 60 percent camphor, and petrolatum is used topically, but the Panel emphasizes that the quantity of phenol released varies with environmental conditions and is not predictable.

Phenol vaporizes slowly, and the vapors may be inhaled. The phenol gains access to the bloodstream via the lungs.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of phenol as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.5- to 1.5-percent concentration of phenol in aqueous solution in the form of a rinse, gargle, or spray not more than three to four times daily. Use a lozenge containing 10 to 50 mg of phenol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 805–809, 1957.

(2) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 987–992, 1975.

(3) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 1263–1264, 1975.

s. *Phenolate sodium.* The Panel concludes that phenolate sodium is safe, but that there are insufficient data available to permit final classification of the effectiveness of phenolate sodium as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has classified phenolate sodium as a Category I anesthetic/analgesic and has described its general characteristics elsewhere in this document. (See part III. paragraph B.1.h. above—Phenolate sodium.)

(1) *Safety.* The Panel concludes that phenolate sodium is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The safety of phenolate sodium has been described elsewhere in this document (See part III. paragraph B.1.h. (1) above—Safety.)

(2) *Effectiviness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of phenolate sodium as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenolate sodium possesses antiseptic and germicidal properties that are similar to phenol (Ref. 1). These actions are due to the phenol that is released when the compound is dissolved in water. It has been applied to bandages in an aqueous solution or with linseed oil in a ratio of 1 part to 5 to 10 parts of oil for use on the skin. It has been used internally for diarrhea and dysentery, but is not recommended due to its toxic properties. The dose used was 0.1 to 0.3 g. It is no longer used for internal purposes.

The sodium salt is formed with the keto form, one of the two hydrogen atoms on position 2 of the benzine ring being replaced by a metal such as sodium (Ref. 2). Phenolate sodium possesses the same antimicrobial properties as phenol. (See part IV. paragraph B.3.r. above—Phenol.)

Phenolate sodium is used topically in oral health care products when it is necessary to have a phenol-containing preparation that is basic and can act as a buffer and still have the activity of phenol.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of phenolate sodium as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a concentration of phenolate sodium in aqueous solution, equivalent to a 0.5- to 1.5-percent concentration of phenol, in the form of a rinse, gargle, spray, or drops, or by swabbing, not more than three to four times daily. For children under 3 years there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products of oral health care containing antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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t. *Povidone-iodine.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of povidone-iodine (PVP–I) as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There is some disagreement concerning the chemical nature of povidone-iodine. Some believe that it is a specific chemical entity; others claim that it is merely a complex. The prevailing consensus is that povidone-iodine is a complex composed of povidone and elemental iodine. Povidone is a faintly yellow solid which dissolves in water to give a plastic-like colloidal solution. Povidone is also known as 1-ethenyl-2-pyrrolidinone polymers; 1-vinyl-2-pyrrolidinone polymers; poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvinylpyrrolidone; polyvidone; and P.V.P. Povidone is made synthetically by interacting 1, 4 butanediol with ammonia and acetylene (Ref. 1).

Povidone was introduced in World War II by the Germans as a substitute for plasma, and as plasma volume expander. A 3.5-percent solution develops osmotic pressure of 400 mm of water. However, it is no longer used for this purpose.

Povidone is available as a series of aggregates having mean molecular weights ranging from 10,000 to 700,000 daltons. Povidone is also soluble in alcohol and chloroform. It is particularly insoluble in ether (Ref. 1). Povidone is used, however, as a solvent for drugs, as a dispersing agent, and to form complexes with various medicinal substances, one of which is iodine. Povidone-iodine is produced commercially by interacting elemental iodine with povidone.

Povidone-iodine consists of yellow flakes which are readily soluble in water. Aqueous solutions have a pH of approximately 2. The addition of sodium bicarbonate makes aqueous solutions less acidic, but also less stable. Freshly prepared solutions of povidone-iodine do not give a blue color with starch as do tinctures and other solutions of elemental iodine. Solutions that have been standing for some time do give a blue color. Aqueous solutions of povidone-iodine are colloidal in nature. Their viscosity varies with the molecular weight of the povidone used to form the complex. When an aqueous solution is applied topically, a slow release of free iodine occurs which exerts an antimicrobial action.

Povidone-iodine is a nonsurfactant type of iodophor and is the only one of this type evaluated by the Panel. Iodophors are complexes of iodine and iodine salts, proteins, and other colloidal organic molecules which release free iodine. They are less irritating to the skin than the tinctures. The iodine that can be released in its free form from povidone-iodine is approximately 10 percent of the total labeled iodine content of the complex.

Elemental iodine is among the most potent antispetics available (Ref. 2). The anticmicrobial effects of iodine are probably due to its iodinating and oxidizing effects on microbial protoplasm. (See part IV. paragraph B.3.n. above—Iodine.) The activity of iodine is reduced by alkaline substances and in the presence of organic matter. This is also true of iodine released from iodophors.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of povidone-iodine as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Povidone is practically nontoxic. Gosselin et al. (Ref 3) rate its toxicity as 1 (practically nontoxic). Povidone has been used as a colloid in salt solutions to increase blood volume in the treatment of hypovolemic shock by intravenous infusion. Povidone is not metabolized. The greatest portion is excreted unchanged by the kidney.

Renal excretion is governed by the size and molecular weight of the particles. Particles whose molecular weights are less than 25,000 daltons are excreted by the kidney. Larger molecules are not filtered by the glomerular membrane or secreted by the tubes of the kidney. Particles of intermediate molecular weight are deposited in the tissues and are slowly excreted over a period of several months to a year. The unexcreted particles are phagocytized by cells in the reticuloendothelial system and stored in the liver, spleen, lung, and bone marrow (thesaurismosis). Such storage has been associated with pathological changes in the lymph nodes. Susceptible individuals who repeatedly inhale substantial quantities, as in hair sprays, and individuals who have used large quantities over long periods of time have been affected and have developed adverse reactions.

Chronic, indiscriminate use of PVP–I has been associated with iodism, an increase in protein-bound iodine, and altered thyroid function. The toxic effects of PVP–I are due to the released free iodine, and since the release occurs slowly its toxicity and irritancy is low. This slow release also raises doubts about its effectiveness, since the active ingredient is elemental iodine.

Recently, Woldkowski, Speck, and Rosenkranz (Ref. 4) have indicated that povidone-iodine is capable of altering DNA in living cells and inducing mutations in salmonella. This is ascribed to the liberated iodine. Because of the known potential and the ability of mutagenic substances to induce cancer in animals, this finding raises serious questions concerning the safety of iodine and iodine-releasing substances used as topical antiseptics on the mucous membranes of the mouth and throat. The halogens, including iodine, are capable of reacting with nucleic acids and their constituents and affecting DNA.

Ferguson, Geddes, and Wray (Ref. 5) recently reported that short-term therapy with a povidone-iodine mouthwash had an adverse effect on 16 healthy individuals after 2 weeks of use. Significant increases occurred in total serum iodide, protein-bound iodine and inorganic iodine, total thyroxine, and free iodine index. The possibility of thyroid suppression following long-term use is also mentioned in this report. The adverse effects of long-term use of potassium iodide are mentioned below. (See Part IX. paragraph B.2. below—Potassium iodide.)

Lagarde, Bolton, and Cohn (Ref. 6) devised experimental models to study the effectiveness of intraperitoneal povidone-iodine in an established peritonitis. In both models there was 100 percent mortality in the povidone-iodine treated group. This study strongly suggests that the intraperitoneal administration of povidone-iodine can be fatal when animals are compromised by peritonitis. The mechanism of this effect is unclear. On the basis of these studies, intraperitoneal administration of povidone-iodine cannot be recommended for therapy of peritonitis.

In another study, Bolton, Bornside, and Cohn (Ref. 7) stated that in dogs with appendicitis-induced peritonitis, intraperitoneal povidone-iodine caused death more rapidly than the instillation of saline solution. The bacterial content of canine peritoneal fluid increased with time, although fewer bacteria were found in fluid from povidone-iodine treated dogs. The differences were not statistically significant. Qualitative chemical analysis of peritoneal fluid revealed iodide but not free iodine. Fifteen to 30 minutes after instillation of povidone-iodine, iodine was present in the peritoneum for 2 hours, but not 3 to 6 hours. The antibacterial effect of povidone-iodine was demonstrated in mice challenged intraperitoneally with lethal doses of *Escherichia coli.* Povidone-iodine diminished mortality, when injected immediately, but not when given 1 to 3 hours later. Immediate injection of povidone-iodine into mice lowered the number of *Escherichia coli* by 3 logs. Injection of povidone-iodine 3 hours after bacterial challenge lowered the number of *Escherichia coli* by only one-third log. This lesser bacterial effect in early treated mice is attributed to greater dispersal and sequestration of bacteria throughout the peritoneal cavity with the inactivation of povidone-iodine by reduction to iodide in vivo. In dogs with appendicitis-induced peritonitis, the more rapid death after treatment with povidone-iodine was not associated with differences in peritoneal microflora, but with peritoneal absorption of excessive amounts of iodide. The ultimate bacterial count in the early treated dogs and those treated with the antiseptic 3 hours after the peritoneal cavity was contaminated

with the same. The mortality likewise was the same.

Although the peritoneum is a serous surface, it does not differ remarkably from a mucous surface. Topical use of povidone-iodine on the peritoneum proved to be of no benefit. It is not unreasonable to assume that this further augments the argument that topical antiseptics on the mucous membranes are of doubtful benefit.

Application of elemental iodine as a tincture to the skin causes direct irritation. On rare occasions iodine gives rise to a hypersensitivity reaction characterized by fever and generalized skin eruptions (Ref. 8). Iodine is rapidly converted to the inactive iodide ion by organic material in the gastrointestinal tract when swallowed.

A study and review of the toxicity of povidone-iodine was performed by Shelanski and Shelanski (Ref. 9), who compared PVP–I to Lugol's solution and tincture of iodine. The three solutions used were formulated to contain equal quantities of free iodine. The oral $LD_{50}$ in rats was 1,300 mg/kg of iodine for the PVP–I complex as compared to 400 mg/kg of iodine for the Lugol's solution. Solutions of PVP–I and tincture of iodine were applied to intact rabbit skin and covered with wax paper. After 24 hours, severe erthema developed, and the paper over the area to which the iodine tincture was applied had to be removed. No reaction was noted 96 hours after application of the PVP–I. The same response was obtained after reapplication 2 weeks later. When the same sequence was carried out on 200 human subjects, similar results were obtained, i.e., a severe reaction to the iodine occurred within 24 hours, and no reaction to PVP–I was observed after 96 hours. Reapplication 2 weeks later also showed no reaction to PVP–I after 48 hours. The PVP–I and Lugol's solution were also tested by daily instillation into the eyes of rabbits and guinea pigs for 2 weeks. PVP–I produced slight reddening which disappeared after 3 days while the eyes instilled with Lugol's solution showed severe erythema, edema, and progressive corneal damage. The investigators concluded from these observations that PVP–I is less toxic, less irritating, and less sensitizing than Lugol's solution or tincture of iodine.

Extensive clinical observations also indicate that PVP–I is generally nonirritating and nonsensitizing when applied to the skin and mucous membranes. For example, Connell and Rousselot (Ref. 10) studies the antiseptic effect of PVP–I applied to the skin of 345 patients either preoperatively, for the treatment of skin infections, or for burns. Additionally, surgeons and ward personnel used PVP–I as a surgical hand scrib. At no time did any patient or physician develop any sensitivity to the PVP–I. Three volunteers used the test preparation one to five times daily for over 2 years with no signs of any injurious reaction. The investigatiors, therefore, concluded that PVP–I was not only highly effective as an antiseptic agent, but also noninjurious to both normal skin and open wounds.

Although two cases of desquamation due to PVP–I used as a preoperative topical antiseptic have been reported by another investigator (Ref. 11), unusual and similar circumstances were noted in each case, i.e., long exposure combined with an elevated body temperature (100° F) resulting from the use of a heating blanket. When these conditions were avoided no further difficulty was encountered.

The marketing experience of industrial products also suggests that PVP–I is relatively nontoxic and nonirritating for use on the skin and mucous membranes. PVP–I has also been widely used by consumers over the past 6 to 7 years with no reports of untoward results (Ref. 12).

The fact that a single application of PVP–I is innocuous on the oral mucosa over a limited area is apparent from reports in the dental literature. However, safety following chronic, long-term use in the entire oral cavity has not been established. Well-controlled studies on the effects of repeated applications on the mucous membranes of the mouth and throat, as would be used in a daily gargle or oral rinse are not available. Six studies are cited in which PVP–I was used as a gargle by a total of over 3,000 patients without untoward effects. In two of these studies, the drug was used more than once (Refs. 12 and 13). In a study that was controlled, no irritation occurred after 2 to 3 applications in 25 patients. The other five studies were uncontrolled. There were insufficient details concerning the experimental design for an evaluation of safety to be made (Ref. 9).

In the opinion of the Panel, PVP–I may be safe for occasional application to the mucous membranes, but there are insufficient data to establish its safe use on a long-term, daily basis as a rinse, mouthwash, or spray on the mucous membranes of the mouth and throat. There is some evidence that long-term use may result in adverse effects from both the povidone and the free iodine that is released (Refs. 12 and 13).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of povidone/iodine as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Povidine-iodine, as is the case with elemental iodine, is effective against both gram-negative and gram-positive organisms. The antimicrobial effect of povidone-iodine is due to release of elemental iodine from the complex. PVP–I is, however, generally less effective than the tincture and other iodine solutions (Ref. 14).

The effectivensss of iodophors against both gram-negative and gram-positive organisms is an advantage over hexachlorophene. The iodophors do not persist in the skin to provide cumulative, continuing antibacterial activity as does hexachlorophene (Ref. 15). The dental and medical literature contains a number of studies suggesting that PVP–I is rapidly germicidal for many oral cavity microorganisms. Its application on the injection site of the oral mucosa prior to administering local anesthesia virtually eliminates all readily cultivable organisms (Refs. 16, 17, and 18). However, it must be remembered that this rapid germicidal action is achieved at an oral site having a relatively small microbial population. The possibility of a carry-over of PVP–I into the culture medium also was not considered in any of the studies reviewed by the Panel.

Three studies indicate that irrigation of the gingival sulcus and rinsing the mouth with PVP–I immediately before tooth extraction or gingivectomy markedly reduces the incidence of associated bacteremia (Refs. 19, 20, and 21). Unfortunately the results of two of these studies have been published only in abstract form, and the data presented are insufficient in detail to be properly evaluated. The third was a study in which 32 patients were treated similarly, one with the povidone-iodine and the other group with an aqueous placebo solution (Ref. 21). Bacteremia occurred in 28 percent of the PVP–I treated group as compared to 56 percent of the placebo group (P is less than 0.01 by chi-square analysis). Cultures taken from gingival sulcus before and after the preoperative treatment indicated that there was some decrease in numbers of microorganisms among the PVP-I-treated group, but since quantitative culture methods were not used, the Panel does not consider these data to be meaningful.

Despite extensive studies on PVP–I applied to the skin, its antiseptic effectiveness in controlling the microbial population was still doubted by the Advisory Review Panel on OTC

Antimicrobial Drug Products for reasons which are also of concern when evaluating it as an oral antiseptic (39 FR 33130–33131). These concerns are as follows:

(i) The rate of "slow-release" of free iodine from PVP–I is variable and not known, particularly in the presence of ill-defined organic material, which may be present on the skin in varying quantities under variable circumstances.

(ii) The germicidal activity of the preparation during the "slow-release" period has not been defined and is not known.

(iii) There is conflicting evidence as to whether PVP–I accelerates or delays wound healing.

(iv) The stability of the preparation during various conditions of storage ge a25my2.254has not yet been determined.

(v) The rate of absorption of the free iodine from the mucous membranes is now known.

(vi) The rate of absorption of the povidone complex with the iodine from the mouth and throat is now known and its potential for producing enlarged lymph nodes has not been determined. The iodine is suspect as a carcinogen, and this, combined with the effect povidone may already have in this regard, are now known.

One study utilizing 262 patients is cited in a product submission (Ref. 12). All but four patients noted symptomatic relief from throat irritation, soreness, dryness, and hoarseness. These evaluations again were subjective and do not provide the Panel with adequate data to make an evaluation.

Povidone-iodine manifests no known topical anesthetic properties which relieve pain due to sore throat and sore mouth.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of povidone-iodine as an antimicrobial agent of the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 7.5-percent concentration of povidone-iodine diluted 1:14 or a 0.5-percent concentration of povidone iodine in the form of a rinse, mouthwash, gargle, spray, or as a swab, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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u. *Secondary amyltricresols.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of secondary amyltricresols as OTC antimicrobial active ingredients for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Amyltricresols are prepared by the interaction of ortho-, meta-, and para-cresols and secondary amyl alcohol at 150° C. This results in a mixture of isomeric secondary amyltricresols. The amyl radical substitutes into the ring. The substitution of alkyl groups into the aromatic ring of a phenolic compound increases the bactericidal effects of the phenol (Ref. 1). The three isomeric cresols have a phenol coefficient of 3, while secondary amyltricresols have a phenol coefficient of 100 or more, depending upon the organism tested. In one study using the FDA method, the mixture had a phenol coefficient of 14 for *Salmonella typhosus* and 100 against streptococci (Ref. 2). These amyltricresols lower surface tension, which allows them to become evenly distributed over cell membrane surfaces (Ref. 3).

The secondary amyltricresols are relatively insoluble in water, but are soluble in alcohol. They are usually dissolved in 30-percent alcohol for use as disinfectants. The presence of environmental proteins, such as blood, serum, mucus, and cellular debris, decreases the bactericidal activity of secondary amyltricresols, but their presence eliminates the bacteriostatic activity completely. Solutions of 1:30,000 inhibit the growth of molds and bacteria. The amyltricresols have been used since 1931.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of secondary amyltricresols as OTC antimicrobial active ingredients for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limits set forth below.

Oral administration of amyl metacresol in rats revealed a slight reddening of the mucosa of the intestines and stomach in doses of less than 1 g/kg. The minimal lethal oral dose in the rat is 2.5 to 4.5 mg/kg (Ref. 4). In a chronic oral toxicity study, rabbits were fed 0.6 g of anyl metacresol without manifestations of toxic symptoms (Ref. 4). The urine and feces were examined daily and no blood, albumin, pus cells, or casts were found. In a study in humans, six subjects were given the drug orally. No toxicity was noted (Ref. 5).

The only human clinical data submitted were from a study in which oral wounds were treated with a commercial preparation containing secondary amyltricresols (Ref. 5). The commercial preparation was compared with standard disinfectants. The amyltricresol preparation was shown to cause no apparent signs of toxicity to the tissues.

No data were available to the Panel concerning the rates of absorption from the mucous membranes of the mouth and throat, irritancy, potential for sensitization, or metabolic fate and elimination of these cresols. Data on tumorigenic, mutagenic, and teratogenic effects of secondary amyltricresols, when used over long periods of time, are not available. There is a paucity of data on chronic toxicity from prolonged use. Little data are available on the long-term use of the lesser known and less frequent use of such phenols. The Panel therefore recommends that they be used only for short-term use.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of secondary amyltricresols as OTC antimicrobial agents for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The secondary amyltricresols are bactericidal in a 1:4 dilution and will kill the following bacteria:

| Bacterium | Time (seconds) |
|---|---|
| *Salmonella typhosa* | 50. |
| *Streptococcus pyogenes* | 20. |
| *Staphylococcus aureus* | 20 to 30. |
| *Diphtheriae pneumonia* | 5. |
| *Alpha-hemolytic streptococcus* | 5. |
| *Diphtheroids* | 20 to 40. |

The same dilution kills *Escherichia coli* and *Pseudomonas aeruginosa* after a 4-minute exposure. *Streptococcus viridans* (alpha-hemolytic streptococci) is killed in 5 seconds and other gram-positive organisms in 5 seconds when exposed to dilutions used in the commercial preparation. Secondary amyltricresols are not sporicidal (Refs. 5 and 6).

The seconday amyltricresols are bacteriostatic. The growth of *Staphylococcus aureus* was inhibited in the presence of plasma after exposure for 5 minutes. The growth of *Streptococcus viridans* was inhibited after exposure for 10 minutes, and the growth of *Salmonella typhosa* was inhibited after exposure for 5 minutes. The growth of a gram-positive sporulating organism was inhibited after 21 hours at a concentration of 1:150 to 1:160 (Ref. 4).

The secondary amyltricresols will kill most gram-positive bacteria and some gram-negative bacteria. No data were submitted demonstrating their effectiveness and bactericidal or bacteriostatic activity against the flora of the oral cavity.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of secondary amyltricresols as antimicrobial agents for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.1- to 0.3-concentration of secondary amyltricresols in aqueous solution in the form of a rinse, mouthwash, or gargle, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

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v. *Sodium caprylate.* The Panel concludes that sodium caprylate is safe, but that there are insufficient data available to permit final classification of the effectiveness of sodium caprylate as an OTC antimicrobial active ingredient for topical use in the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Sodium caprylate is the sodium salt of caprylic acid (octanoic acid) ($Ch_3(CH_2)_6COONa$), an aliphatic, straight-chained carboxylic acid. It is the salt of a lower molecular weight fatty acid and may be considered to be a soap of an eight-carbon, fully saturated acid. Sodium caprylate may be prepared by neutralizing caprylic acid with sodium carbonate or sodium hydroxide. It is freely soluble in water and sparingly soluble in alcohol (Ref. 1). It is poorly ionized to the sodium and caprylate ions in water. Sodium caprylate is one of several fatty acids, such as undecylenic and propionic, that have been used as fungistatic agents topically.

Sodium caprylate has been used as a fungicide and fungistatic agent for the treatment of thrush, tinea pedis (athlete's foot), tinea cruris (jock itch), and other superficial fungous infections of the skin and mucous membranes, particularly those due to trichophyton, microsporon, and candida (Ref. 1). Both the acid and salt were used in the treatment of candidiasis before antibiotics became available. The salt has had limited usage in dentistry as a component of an endodontic medication advocated by Grossman and Christian (Ref. 2), Fajarda, Grossman, and McShane (Ref. 3), and Sawinksi and Gurney (Ref. 4). They reported that it inhibited the growth of *Candida*

*albicans* in concentrations of 0.03 to 5.0 percent.

Sodium caprylate has also been shown to be effective in the treatment of athlete's foot, when applied in the form of a 10-percent ointment (Ref. 5). It has been used as a dusting powder in a strength of 10 percent, in an inert powder, either along or with other octanoates. Aqueous solutions of 5, 10, and 20 percent sodium caprylate have been administered topically to the skin or mucous membranes. A 5-percent solution has been used as a douche and 10 to 20 percent solutions have been used in the oral cavity.

(1) *Safety.* The Panel concludes that sodium caprylate is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There are few data on animal or human toxicity of sodium caprylate. However, since the fatty acids appear in many foods and are consumed as such, it is the consensus of the Panel that sodium caprylate, likewise, is safe.

Cohen (Ref. 6) reported using sodium caprylate in a concentration of 50 mg/mL orally and intravenously to treat albino rabbits infected with *Coccidioides immitis.* After sacrificing the animals, postmortem examinations revealed no pathologic effects in any organ in any of the animals. In the same study, 3-g doses of 5 percent sodium caprylate in 5 percent glucose were administered to human subjects intravenously every day for 3 months. The maximum dosage given was 8 g per day. As was the case in the aminal study, no adverse drug reactions occurred.

Cohen and Persky (Ref. 7) have reported treating a series of 12 cases of thrush with a 10-percent aqueous solution of sodium caprylate. The infections responded favorably to the treatment. There were no adverse reactions noted to the drug nor were there any recurrences among the 12 individuals treated. They also reported using 10 percent aqueous sodium caprylate as a routine hospital treatment in both nurseries as well as in the outpatient department.

It is the belief of the Panel that when taken internally, sodium caprylate would probably be metabolized in the same manner as other fatty acids, and that catabolic fatty acid pathways are utilized. No unique toxicity would be expected.

In marketing experience dating back to 1963, 20 nonspecified adverse reactions have been reported (Ref. 9).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of sodium caprylate as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Like other soaps, sodium caprylate acts as a surfactant, detergent, and emulsifier. This action is due to the caprylate ion, which is an anion. Keeney (Ref. 8) overcame infection of thrush due to *Candida albicans* by local swabbing of lesions of the entire mouth three times daily with a 20-percent aqueous solution of sodium caprylate. Thrush is a mycotic disease of the mouth, throat, and upper digestive tract. (See part II. paragraph B.4.b.(8) above—Candidiasis.) It is characterized by the formation of white plaques within the oral cavity, often coalescing to form a false membrane on the mucosa. It occurs more commonly in debilitated persons.

Cohen and Persky (Ref. 7) confirmed Keeney's findings. They reported dramatic results in 12 cases using a 10-percent aqueous sodium caprylate solution rubbed on the buccal and lingual tissues four times daily. Four days was the average time required to rid the mouth of the fungus. The 10-percent solution benefited all 12 cases of thrush and appeared to cure the infection with no complications or recurrences.

Cohen (Ref. 6) studied the effects of sodium caprylate and three other fungicides on *Coccidioides immitis* using in vitro studies. The fungicidal concentration of sodium caprylate ranged between 19 and 150 mg/mL. In addition, in vivo studies on albino rabbits were performed using 50 mg/mL orally and intravenously per 2.5-kg animal. Cohen concluded that sodium caprylate is effective on the mucous membranes of the mouth and throat and also in sinuses harboring coccidioidal spherules.

A sodium caprylate ointment was shown to have fungistatic activity and possess antibacterial action against *Staphylococcus aureus* and beta-hemolytic streptococcus, though in this respect the ointment is inferior to one prepared from propionic acid and propionate (Ref. 9).

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of sodium caprylate as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 10.0- to 20.0-percent concentration of sodium caprylate in the form of a spray or by swabbing onto lesions in the mouth and throat, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Date Required for Evaluation.)

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(1) Council of the Pharmaceutical Society of Great Britain, "British Pharmaceutical Codex," The Pharmaceutical Press, London, pp. 698–699, 1954.

(2) Grossman, L. I., and C. K. Christian, "End-Point Study of Bactericidal Effect of Antibiotics Used in Endodontics," *Journal of Dental Research,* 31:42–46, 1952.

(3) Fajarda, O. P., L. I. Grossman, and J. McShane, "An In Vitro Study of Antiseptics and Antibiotics Used in Endodontics," *Journal of Dental Research,* 35:656–659, 1956.

(4) Sawinski, V. J., and B. F. Gurney, "Antifungal Evaluation of a New Endodontic Antiseptic," (abstract), *Journal of Dental Research,* 43:749, 1964.

(5) Keeney, E. L., et al., "Sodium Caprylate: A New and Effective Treatment for Dermatomycosis of the Feet," *Bulletin of Johns Hopkins Hospital,* 77:422–436, 1945.

(6) Cohen, R., "Four New Fungicides for Coccidioides immitis: 1. Sodium Caprylate. 2. Ethyl Vanillate. 3. Fradicin. 4. Thiolutin," *Archives of Pediatrics,* 68:259–264, 1951.

(7) Cohen, R., and M. Persky, "Sodium Caprylate Treatment for Thrush," *Archives of Pediatrics,* 68:33–34, 1951.

(8) Kenney, E. L., "Sodium Caprylate: A New and Effective Treatment for Moniliasis of the Skin and Mucous Membranes," *Bulletin of the Johns Hopkins Hospital,* 78:333–339, 1946.

(9) Osol, A., et al., "The Dispensatory of the United States of America," 24th Ed., J. B. Lippincott Co., Philadelphia, p. 1588, 1947.

w. *Thymol.* The Panel concludes that thymol is safe, but that there are insufficient data to permit final classification of the effectiveness of thymol as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol, also known as thyme camphor, is methyl isopropyl phenol. It is therefore an aromatic alcohol. Thymol

possesses topical anesthetic/analgesic properties and has been described elsewhere in this document. (See part III. paragraph B.3.c. above—Thymol.)

(1) *Safety.* The Panel concludes that thymol is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The safety of thymol has been described elsewhere in this document. (See part III. paragraph B.3.c.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of thymol as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The assumption has been made the because thymol is a constituent of one of the various "volatile oils" used in the mouth and throat, it is an effective antimicrobial agent. Its activity is presumably due to its lipophilic properties, which favor penetration into the cell membrane. A 1- to 5-percent solution of thymol in alcohol is used on the mucous membranes to treat herpes. Sollmann (Ref. 1) states "its actions are similar to those of phenol." Thymol's bacteriostatic efficiency is higher than that of phenol in restraining the growth of "pus organisms" in a 1:3,000 dilution. Sollmann also states that "it is not a very effective germicide" and that "thymol has a pleasant clean taste." The text also states that "a saturated watery solution makes a rather agreeable and fairly efficient antiseptic and deodorant mouthwash or gargle, and lotion for discharging wounds."

Thymol has a high phenol coefficient (25), but its antimicrobial activity is greatly impaired by the presence of organic matter (Ref. 1). For instance, the addition of dried feces to an antimicrobially active solution reduces the activity of thymol by two-thirds. It reduces that of phenol by one-third. Thymol is active against yeasts, molds, and fungi. It has been used to treat fungal skin infections with fair success.

Esplin (Ref. 2) writes that, "Thymol and its derivatives, principally chlorothymol, possess both bactericidal and fungicidal properties." Thymol is chiefly of value as a fungicide. It was formerly employed as an anthelmintic, administered orally against certain worms.

The "United States Dispensatory" (Ref. 3) states that "thymol was introduced as a disinfectant with uses similar to those of phenol but with the advantage of having a more agreeable odor. In the absence of organic matter, it is more potent than phenol, but in the presence of large amounts of proteins its activity is greatly reduced." Because of this reduction in activity and because it is a strong irritant, thymol is of little value for use on open wounds or on the mucous membranes of the mouth and throat. Thymol is fungicidal and may be used in the treatment of a variety of fungous infections of the skin. Thymol was formerly used for its antiseptic action in the stomach and intestines. It stimulates peristalsis and may cause diarrhea. Thymol is absorbed from the intestine when ingested orally. About 50 percent of it is conjugated with glycuronic and sulphuric acids, and the conjugate is excreted into the urine.

In a submission to the Panel, a mixture of thymol, menthol, eucalyptol, and methyl salicylate was tested for antimicrobial activity (Ref. 4). It was allegedly found that thymol possessed antimicrobial activity. The testing was not performed using the individual ingredient but by removing the thymol from the mixture and determining the effectiveness of the mixture when the thymol was not present. The mixture, minus thymol, had less antimicrobial activity than when thymol was present. The Panel does not consider these data to be proof of the effectiveness of thymol as an antimicrobial agent when used as a single ingredient.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of thymol as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.006- to 0.1-percent concentration of thymol in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 227–228, 1957.

(2) Esplin, D. W., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 1037, 1970.

(3) Osol, A., et al., "The Dispensatory of the United States of America," 1950 Ed., J. B. Lippincott Co., Philadelphia, pp. 1218–1219, 1950.

(4) OTC Volume 130136.

x. *Thymol iodide.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of thymol iodide as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol iodide is also known as dithymol diiodide (Ref. 1). Thymol iodide was originally considered to be official and was listed in the "United States Pharmacopeia." It is a red-yellow or red-brown powder. It is made by treating a solution of thymol with potassium iodide and sodium hydroxide. Two molecules of thymol interact with one molecule of iodine, and the hydrogen atom on the hydroxyl group of each thymol molecule is substituted with an iodine atom. Thymol iodide has a slightly aromatic odor. It is insoluble in water, glycerin, carbon disulfide, and liquid paraffin; it is soluble in chloroform, ether, collodion, and oils, and slightly soluble in alcohol. Thymol iodide must be protected from light. If exposed to light it undergoes decomposition to free iodine and iodinated derivatives of thymol. Thymol iodide is incompatible with ammonia, mercury bichloride, hydroxides of potassium and sodium, and their carbonates. It gives off vapors of iodine when heated above 100° C.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of thymol iodide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

When thymol iodide is applied to tissues, it slowly releases thymol and iodine. This is the basis of its alleged antimicrobial action. It behaves like an iodoform in this respect. Data on the

$LD_{50}$ in animals and on human toxicity were not available to the Panel. The Panel assumes that the toxic effects, if ingested orally, would be due to, and be similar to, those of free iodine. Thymol iodide contains 53 percent iodine by weight. When used externally in dusting powders, it is considered to be nontoxic. Data on systemic toxicity, particularly after long-term use, were not available to the Panel (Ref. 2). Recent evidence indicates that long-term use of iodine-releasing compounds may be mutagenic and alter thyroid function by causing increased activity at first and suppressed activity later. The Panel cautions that this may also occur with long-term use of thymol iodide.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of thymol iodide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol iodide is similar to iodoform in its properties and behavior. The compound is a water-insoluble, reddish-brown bulky powder containing 43 percent iodine. It is used as an antiseptic dusting powder. It was sometimes employed in an ether solution in which form it has been successfully used as a 25-percent concentration in ether for the treatment of chancroid ulcers. Thymol iodide is effective against *Staphylococcus aureus.*

Thymol iodide is one of the few drugs which are effective in the treatment of actinomycosis. It has been used for this purpose to treat skin lesions. Thymol iodide has also been used in ointments in concentrations ranging from 2 to 10 percent. It has been used externally as an antimicrobial agent and internally as a source of iodine.

The Panel concludes that there is insufficient evidence from controlled studies to establish the effectiveness of thymol iodide as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 2- to 10-percent oil solution of thymol iodide by swabbing or applying digitally to the affected area, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling).

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1214, 1976.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, PA, p. 817, 1948.

y. *Tolu balsam.* The Panel concludes that tolu balsam is safe, but that there are insufficient data available to permit final classification of the effectiveness of tolu balsam as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

(1) *Safety.* The Panel concludes that tolu balsam is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

The characteristics and data on the safety of tolu balsam are described elsewhere in this document. (See part IX. paragraph B.3.c(1) below—Safety.)

One manufacturer (Ref. 1) submitted the premise that "tolu balsam is well known abroad in preparations for the treatment of sore throat." However, no supporting data were given.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of tolu balsam as an OTC antimicrobial ingredient for topical use on the mucous membranes of the mouth and throat.

Tolu balsam is a naturally occurring mixture of resins, volatile oils, and organic acids. It contains 12 to 15 percent free cinnamic and benzoic acids and approximately 40 percent benzyl esters of these acids (Ref. 2). It contains a concentration of 1.5 to 3 percent volatile oils. The effectiveness of these acids, esters, and volatile oils as antimicrobial agents is unknown. Benzoic acid has been evaluated by the panel and placed in Category III as an antimicrobial activity. The Panel has likewise considered the antimicrobial activity of volatile oils. In view of the fact that their composition is so variable, the Panel concludes that it is impossible to classify them as effective antimicrobial agents. (See part IV. paragraph A.9. above—Volatile oils.)

Tolu balsam has a feeble stimulating expectorant activity and formerly was used widely in the formulation of various cough syrups (Ref. 2). It is usually employed in the form of tolu balsam syrup which was once official and was included in the "United States Pharmacopeia" and "National Formulary." The balsam is an ingredient found in the compound benzoin tincture. Inhalation of the vapor generated by heating the balsam was also used for the treatment of respiratory infections. Tolu balsam has been employed occasionally in the treatment of contaminated wounds for its "stimulating and antiseptic" activity. No data are supplied indicating the spectrum and the degree of antimicrobial activity. It has also been used for scabies (Ref. 3).

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of tolu balsam as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage for tolu balsam.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

**References**

(1) OTC Volume 130052.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 126, 1976.

(3) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1236, 1975.

(4) Osol, A., et. al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 1440–1441, 1955.

## Category III Labeling

*Proposed indication.* "For the temporary relief of minor sore mouth and sore throat by decreasing the germs in the mouth."

*C. Data Required for Evaluation*

The Panel agrees that the protocols recommended in this document are in keeping with the sciences of pharmacology and theraupeutics and the art of medicine and do not preclude improvements in methods for obtaining data that might be developed in the future.

1. *General principles in the design of experimental protocols for testing antimicrobial agents.* The Panel has reviewed the data submitted for antimicrobial active ingredients in OTC oral health care products for topical use on the mucous membranes of the mouth and throat. The Panel has made the suggestions outlined below concerning requirements for protocols for conducting studies to obtain data for reclassifying Category III antimicrobial active ingredients to Category I for safety or effectiveness or both.

The Panel has identified and evaluated two categories of products containing antimicrobial active ingredients; those used on a short-term basis to relieve symptoms of sore mouth or sore throat or both due to microbial infections and those used on a long-term, often on a day-to-day, basis, for cleansing the mouth, suppressing mouth odors, and other related purposes in which no symptoms of an infectious process are evident but for which use antimicrobial claims are made. The ingredients in formulations evaluated in both categories of products include rinses, gargles, sprays, drops, and other solutions for local application, ointments, lozenges, troches, and powders. The method of application and usage may introduce variable factors that must be given consideration in preparing protocols for evaluation of an ingredient. The Panel recognizes that antimicrobial-containing oral health care products are intended to be used to treat and relieve symptoms due to inflammatory processes and that these pathologic states have diverse etiologies. Therefore, it is impossible to propose a single general protocol that would yield data to substantiate claims for safety and effectiveness made for all antimicrobial ingredients submitted for consideration. Obviously, appropriate individual tests must be devised or chosen that adequately establish the safety and effectiveness of an ingredient for a claimed indication or several claimed indications on the labeling.

The Panel expects that the data obtained from the chosen tests show that preparations applied to the mucous membranes of the mouth and throat act topically and reduce pathogenic microbial populations to levels that are therapeutic and that relieve symptoms caused by the infection. The Panel is aware of the fact that differences in usage may introduce uncontrollable, variable factors that make testing difficult.

In its evaluation of the clinical effectiveness of these antimicrobial ingredients, the Panel was aware of the fact that they enjoy widespread OTC use for treatment of pathologic states of the mouth and throat due to amtimicrobial activity. The Panel also recognizes that the consumer has the right to self-diagnosis and self-treatment. The Panel concedes that the average consumer may, in most cases, recognize the signs for symptoms of occasional minor infections in the mouth and throat and should therefore have the option of using an OTC medication for short-term treatment. The Panel believes this should be the case provided the consumer is fully protected by warnings in the labeling, should the symptoms be due to a serious illness not amenable to use of OTC antimicrobial agents, and that the manufacturer has clearly and convincingly demonstrated justification for the claims for such use. The Panel is willing to recommend acceptance of realistic therapeutic labeling claims for effectiveness in treatment of minor, occasional, self-limited infections for short-term use.

The Panel expects the data submitted to demonstrate that the relief of symptoms is due to the antimicrobial effects of an ingredient and that the symptoms recede and may even ultimately disappear after the recommended periods of application.

Demonstration of clinical effectiveness must include proof that the formulated topical antimicrobial product is more effective than the vehicle in which the ingredient is incorporated. The Panel recommends controlled studies that demonstrate that each active ingredient in a combination product for which an antimicrobial claim is made does indeed manifest the antimicrobial activity that is claimed and is not merely an inert vehicle or substance inducing a beneficial placebo effect in the mouth and throat. The Panel requires that evidence be submitted to verify that each antimicrobial agent is successfully released from its vehicle when applied to mucous membranes and thereby becomes available to act on microorganisms within the mucosal layers to which they are applied or with which they come into contact.

2. *Methods of study.* The Panel recognizes that three areas of effectiveness of an ingredient may have to be evaluated: (a) Effectiveness in the treatment of infections by an antimicrobial action. This is a mandatory requirement for study since these claims are made for all antimicrobial agents reviewed. (b) The effectiveness on wound management. By "wound management" the Panel is referring adverse effects on healing or beneficial effects on healing. It must be shown that delays in healing of ulcerations and sloughs of the mucosa caused by the ingredient do not occur. Claims that an ingredient promotes or accelerates wound healing must be substantiated by appropriate, convincing tests and data. (c) Effectiveness for propfhylaxis. It a prophylactic claim is made for an ingredient, the symptoms or pathologic process that are prevented from developing and the types of microorganisms that are killed or prevented from proliferating must be identified. It must be shown that the claimed prophylaxis does indeed occur.

The Panel recognizes that difficulties may be encountered in obtaining acceptable in vivo data concerning specific antimicrobial activity which can be used to establish effectiveness. Therefore, the Panel suggests that preliminary well-designed and well-controlled in vitro studies be performed, the data of which can be verified and supported by in vivo animal and human model studies. Human model studies should be followed by appropriate clinical trials. Such investigational models should simulate as closely as possible situations that would be encountered in actual clinical practice.

The recommendations outlined above and below for testing of effectiveness are not intended to be mandatory requirements. They are presented merely to indicate the types of data considered necessary and to provide suggestions for obtaining such data. It is the consensus of the Panel that the responsibility of selecting or devising reliable methods for procuring acceptable evidence of effectiveness of an ingredient rests with the individuals sponsoring or promoting the product and not with FDA.

a. *In vitro testing.* In vitro testing should include the following: A technique that insures that a carryover of the antimicrobial ingredient into the test system is eliminated by proper dilution or inactivation of the ingredient;

Determination of the spectrum of antimicrobial activity of the agent using both standard cultures and recently isolated strains of each microbial species;

Determination of the minimal inhibitory concentration (MIC) of the antimicrobial agent under standard conditions and against standard reference organisms; and

Testing freshly obtained clinical isolates from mouth or throat infections to provide updated, relevant data on susceptibility of these isolates to an antimicrobial agent.

The Panel has described below an in vitro test that may be found useful as a guide in formulating required protocols for specific ingredients submitted to this Panel for review which have been placed in Category III.

Antimicrobial oral health care products are tested to determine the ability of an active ingredient in a product to kill an axenic population of specific organisms by the following method:

(1) *Test organisms.* (i) *Streptococcus mutans,* ATCC number 25175

(ii) *Actinomyces viscosus,* ATCC number 19246

(iii) *Candida albicans,* ATCC number 18804

(iv) *Pseudomonas aeruginosa,* (optional) ATCC number 10145

(2) *Stock cultures.* Cultures of American Type Culture Collection (ATCC) origin are subdivided and lyophilized or frozen at −25° C or lower to provide standard stock cultures for future use. The optional culture may be used if it is desirable to test a gram-negative bacterium.

(3) *Test cultures.* A stock culture of each species is first revitalized and then transferred to fresh brain heart infusion (BHI) broth, in order to initiate a battery of tests. The cultures are transferred to fresh BHI broth for two successive days following the first transfer. All incubations are to be carried out at 37° C. It is suggested that the *Actinomyces viscosus* and *Streptococcus mutans* be cultured anaerobically, the *Candida albicans* cultured aerobically. It is suggested that the candida and strepotococcus cultures be incubated for 16 to 18 hours; the actinomyces culture for 32 to 36 hours, so as to be able to compare tests from one laboratory to another.

(4) *Test medium.* Letheen broth or another inactivating medium (to eliminate carry over of active components) is prepared and dispensed in 9.9-mL quantities in unlipped culture tubes, capped with closures or plugged with cotton and then autoclaved.

(5) *Reaction tubes.* Sterile, unlipped test tubes, capped with closures or plugged with cotton, are used for mixing the cultures in the mouth rinse or mouth rinse components in the test.

(6) *Temperature of the test.* The oral health care product, as commercially available, or each active ingredient at the product concentration, in a suitable inactive vehicle, and the test culture must be brought to temperature equilibrium in a water bath at 37° C and held at this temperature throughout the test.

(7) *Test method.* (i) One milliliter of the test culture and 9 mL of the product or active ingredient (as noted above) are mixed rapidly and thoroughly. A stopwatch is started at the time of mixing.

(ii) At 1 and 2 minutes, 0.1 mL of the raction mixture is aseptically removed and inoculated into the tubes of the inactivating medium and mixed.

(iii) These tubes are incubated at 37° C for 48 hours. At this time, the entire contents of the culture tubes which exhibit no growth are aseptically transferred to 90 mL of sterile inactivating medium, to further dilute any carry-over of active ingredients(s). If upon further incubation for 1 week at 37° C no growth is detectable, the test microorganisms will be considered to have been killed by the test oral health care product or its ingredients.

(iv) As a control on the viability of the test organisms, 1 mL of the test culture is diluted in 9 mL of BHI broth and 0.1 mL of this mixture is added to inactivating medium (with no test product or ingredient) and incubated at 37° C.

(v) Replicate test samples must be done and must exhibit reproducibility.

(vi) A reference (positive) standard control is necessary to validate the test procedure by assuring the consistent susceptibility of the test organisms. Chlorhexidine digluconate, 0.2 percent in sterile water, is acceptable for this purpose.

(8) *Test in the presence of biological fluids.* Antimicrobial agents are subject to dilution with secretions in the mouth and throat. Saliva, crevicular fluid, and serum are the biological fluids of the mouth and throat which may exhibit inactivating effects on antimicrobial agents. Sterile whole human saliva, i.e., membrane filter saliva, would appear to be the ideal test mouth secretion because it is the principal oral biological fluid, but it is not recommended for use because it cannot be standardized from one laboratory to another. Sterile fetal calf serum is used instead of saliva because it possesses similar proteinaceous inactivation characteristics, few antibodies or antimicrobial components, and may be obtained commercially in standardized forms. It may be necessary to omit the addition of serum to the reference standard control, e.g., chlorhexidine, because serum, in some instances, inactivates the antimicrobial agent. The effect of serum on the product or test ingredient must be demonstrated.

The oral health care product, as commercially available, and each active ingredient at product concentrations in a suitable active vehicle are tested in the presence of a standardized biological fluid as follows:

(i) Two milliliters of sterile fetal calf serum is added to 2 mL of test organism and tested. Two milliliters of the mixture is added to 8 mL of the product or active ingredient and mixed (as noted above).

(ii) The mixture is tested as previously described under "Test method."

(9) *Evaluation.* An active antimicrobial ingredient will have passed the in vitro test if it kills all the test organisms, in the presence and in the absence of serum, within 2 minutes. Results of the test at 1 minute will be provided for information only and will not be used for comparison among products or ingredients. The 2-minute exposure time reflects the contact time of the antimicrobial product or ingredient in vivo, before it is diluted by saliva and other oral biological fluids.

b. *In vivo testing.* In vivo testing should be designed to closely approximate the clinical situations for which a product is intended to be used and to substantiate claims in the labeling that the relief of symptoms of mouth and throat infections is indeed due to an antimicrobial activity of an ingredient. A well-designed study should demonstrate that the antimicrobial effect is due to the agent itself and not to the vehicle. Control groups should receive treatment with inert vehicles which are identical in appearance, color, and consistency to the test material. A double-blind procedure should be employed to minimize bias in making observations and in reporting results. An appropriate procedure to insure the random allocation of subjects to treatment and the comparison of groups should be employed. In vivo testing, including animal and human models, should be performed prior to clinical studies.

The Panel is aware of the difficulty in conducting large-scale prospective clinical trials, and, therefore, suggests that statistical methods, such as the use of sequential designs, may be used in limiting the sample size.

The Panel is aware of the fact that some microbiologists have relied upon reduction of deposits of plaque on the teeth as an index of effectiveness of antimicrobial ingredients used in oral health care products for treating symptoms of sore mouth and sore

throat. Elsewhere in this document appears a discussion of plaque reduction and its relationship to antimicrobial activity and the fact that the Panel concludes that no correlation can be established between reduction of plaque and the relief of symptoms of sore mouth and sore throat. (See part IV. paragraph A.6. above—Evaluation of antimicrobial activity.) Likewise, the Panel concludes that there is no correlation between plaque reduction and the effectiveness of antimicrobial agents in oral health care products for prophylactic use. The Panel, therefore, does not acept data on effectiveness of antimicrobial agents in oral health care products based upon their ability to inhibit plaque formation.

(1) *Human models for treatment.* It is obvious to the Panel that no reliable, satisfactory, safe, investigational models presently exist or can be devised for producing infections experimentally in the oral cavity that simulate symptoms that would be encountered clinically for testing the effectiveness of antimicrobial oral health care products. The Panel recognizes that no single protocol or test system can possibly be devised that provides proof of effectiveness for all therapeutic applications for which OTC topical antimicrobial agents are intended. Separate protocols will have to be designed to consider individual claims or groups of similar claims and to determine such factors as the antibacterial spectrum, the duration of antimicrobial action, and the effectiveness of a product or ingredient for a particualr therapeutic indication.

(2) *Wound healing.* The Panel recognizes that the determination of the effects of an ingredient on wound healing, particularly in human subjects, is difficult. Animal models with artificially contaminated wounds have been used by some investigators. However, if animals are used, these ingredients must be further tested for this attribute in human clinical trials. There is a need for the development of procedures to determine whether or not antimicrobial oral health care products topically applied to minor ulcerations and mucosal wounds exert adverse effects and delay healing in man. The Panel suggests that such protocols and study designs should be developed in consultation with FDA.

The subjects selected for such studies should have ulcerations and other open lesions in the mouth and throat that are appropriate for testing a Category III ingredient. The Panel suggests that in designing such protocols in clinical studies the characteristics of the lesion, such as color, size, amount of exudate or purulent discharge, degree of edema, and rate of epithelization should be noted at appropriate intervals. The drug should be applied in such quantities and with the same frequency as stated in the labeling. Its effects should be compared with a control. The changes in the size, color, and appearance of a wound area can be followed by serial photographs or by planimetry or both.

3. *Selection of patients.* The final appraisal of the effectivness of a topical antimicrobial agent must be undertaken in a clinical setting under circumstances conforming to actual conditions existing in a target population for which use of the product is intended. Testing must conform to accepted ethical standards. Animal and human models may lessen the need for extensive, time-consuming, expensive clinical trials on agents that are found to be effective in model systems. The Panel, however, expects that whatever clinical studies are undertaken should be adequate to confirm the resuts of model studies. Testing of the complete formulation for effectiveness will be required to judge the importance of the vehicle in the release of the active ingredients as well as the influence that the formulation exerts on effectiveness and safety.

4. *Interpretation of data.* The recommended dose of an antimicrobial agent should induce a statistically significant reduction of symptoms or a positive amelioration of a disease process when compared with a placebo response.

Evidence of drug effectiveness is required from both in vitro and in vivo testing based upon the results of two or more independent investigators or laboratories. All data submitted to FDA must present both favorable and unfavorable results.

5. *Determination of safety.* Tests for safety must be topical and systemic. These have been mentioned elsewhere in this document. (See part II. paragraph C.2. above—Testing for recategorization of Category III ingredients.) They are specifically mentioned in more detail here due to the cytotoxic nature of many of the antimicrobial ingredients. It is known that some antimicrobial drugs that kill microorganisms may in most cases injure some cells of the host. For this reason the local effects must be defined. Also, these drugs are readily absorbed from the mucous membranes and can act systemically. Systemic toxicity is therefore an important consideration particularly when they are advocated for long-term use on a day-to-day basis for years or even over the span of a lifetime as would be the case when using mouthwash and gargle preparations.

a. *Topical safety testing.* The primary irritation potential of an ingredient following acute and subacute exposures must be determined. Special attention should be devoted to the effects on the mucous membranes of the mouth and throat.

The potential for development of topical allergic reactions following short- or long-term exposure must be determined.

The potential for development of photosensitivity must be determined.

The effect on wound healing must be determined, particularly any inhibitory effect.

The effect of subsensitivity or accumulation of an ingredient on the mucous membranes must be determined.

The above tests should be performed using each ingredient in pure form, individually, if they are in a combination, as well as the final complete formulation to judge the effect of the vehicle in the release of the active ingredients.

b. *Systemic safety testing.* The Panel requires the qualitative and quantitative determination of metabolites in biologic tissues and secretions in cases where it deems the data are essential if not available. The Panel recommends the development of adequate chemical, analytic, or bioassay techniques if not available.

The determination of the degree of absorption through the mucous membranes by measurement of blood levels is required after acute exposure as well as after chronic usage and exposure. If the product is an aerosol, adequate inhalation studies should be conducted to determine the quantity inhaled and systemic effects and accumulation in blood and tissues.

The target organ or organs susceptible to the toxic effects of the drug and the quanitity causing these effects should be determined. Toxicity should be correlated with blood levels and half-life of the drug. If a toxic effect develops, the blood levels causing such toxicity should be determined in several species. The maximal lethal dose and the minimal lethal dose and the $LD_{50}$ should be determined in animals. Tissue distribution, metabolic rates, metabolic fate, and routes of excretion should be determined in cases where the Panel so recommends, if such data are lacking and deemed essential.

The Panel is unable to comment on the tumorigenicity, mutagenicity, or teratogenicity of the ingredients it has evaluated with the data it has available. The possibility that they do exert these

effects cannot be disregarded even though many of these drugs have been in use for many years. The Panel however, does not expect the sponsor of a product to conduct studies to obtain such data if they are not available since these involve complex studies and are conducted by the National Cancer Institute (NCI) and other agencies equipped for such investigative work.

*D. Minority Report on Antimicrobial Agents*

The goal of the Advisory Review Panel on OTC Oral Cavity Products was to determine if drugs used in the oral cavity and purchased over-the-counter by the consumer are safe and effective. A final report was written and, because portions of it are deficient in the opinion of a minority of the Panel, the following minority report is offered.

1. *Restrictions on the scope of investigation.* The charge of the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel) was restricted to an investigation of those liquid, gel, or solid drug formulations for use in the oral cavity that were not used for symptomatic relief of colds, cough, or related upper respiratory disease. A further restriction was that the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Dental Panel) was charged to investigate the safety and effectiveness of all oral drugs that were dentifrices, fluorides, and other antidental-plaque drugs, as well as those products used to treat oral mucosal injuries. As time passed the Dental Panel deferred consideration of the antiplaque claims. These restrictions meant that the scope of investigation of the Oral Cavity Panel was limited to the area of mouthwashes, mouth rinses, oral lozenges, gels, and other drug formulations used either to relieve symptoms of general diseases or to maintain oral hygiene.

It was an exceedingly complex problem to determine the effectiveness of mouthwashes and similar drugs, because such OTC preparations are generally not used to cure or alleviate specific oral diseases.

The antimicrobial oral cavity products, especially the antimicrobial mouthwashes, have only recently included the "antiplaque" claim in their labeling and advertising. They are used today to refresh the breath and by some consumers in an attempt to prevent the two most common and widespread diseases of the oral cavity: dental caries and periodontal disease. This use by the consumer is a recent one because of advertising and is directed toward the reduction in dental plaque by mouthwash formulations that contain antimicrobial agents.

The antiplaque activity of antimicrobial mouthwashes and mouth rinses was a parameter that the Oral Cavity Panel believed, during the first 4 years of its tenure, was a reasonable parameter to measure the antimicrobial activity of the drugs. The Dental Panel for a while considered the antiplaque claim of oral drugs, but in its later stages deferred this scope of investigation to the Oral Cavity Panel. In its last year of activity, the majority of members on the Oral Cavity Panel suddenly abandoned consideration of the antiplaque activity. The decision to abandon investigation into the antiplaque claim created a condition where none of the OTC advisory panels had jurisdiction over antiplaque claims. It may have been that the espousal of the Oral Cavity Products Panel stimulated the advance of antiplaque claims by manufacturers of antimicrobial mouthwashes. The sudden reversal of the Panel and abandonment of consideration of such claims creates an unfortunate situation in which no OTC advisory panel has jurisdiction over antiplaque claims and manufacturers of antimicrobial mouthwashes have no direction or guidelines to prove the effectiveness of their formulation in killing bacteria in the oral cavity.

2. *Guidelines to determine the effectiveness of antimicrobial mouthwashes or mouth rinses in the laboratory.* In 1977, the Oral Cavity Panel approved guidelines for the in vitro and in vivo effectiveness of antimicrobial mouthwashes. (See part IV. paragraph D.5. below—Proposal for the antimicrobial evaluation of oral cavity products.) These guidelines were established after consultation with experts in academia, in government, and in industry. The guidelines were constructed to be procedures that were in harmony with the existing body of knowledge relating to the role that bacteria play in dental caries and periodontal diseases. The in vitro procedure was based on the approved methodology employed for the general assay of antimicrobial drugs (Ref. 1). The in vivo procedure was based on reduction of plaque formation. These guidelines were intended to present general procedures that would enable drug manufacturers to reasonably demonstrate the effectiveness of antimicrobial mouthwashes.

The procedures developed by members of the Panel were intended to be guidelines, based on the present "state of the art" procedures. If advances were made in the future in the "state of the art" in either in vitro or in vivo procedures, it was expected that the newer and improved methods would be used at that time to test effectiveness of the drugs.

One consideration in designing the in vitro guidelines concerned recent evidence that in animal models, certain dental diseases involved with dental plaque have a specific bacterial component. This was reflected by the choice of *Streptococcus mutans,* ATCC number 35175, serological group C; *Actinomyces viscosus,* ATCC number 19246; and *Candida albicans,* ATCC number 18804. These test organisms are representative of the pathogenic oral bacteria and fungi. *Streptococcus mutans* and *Actinomyces viscosus* represent supragingival plaque-inhabiting bacteria that have been shown repeatedly to be caries-inducing in animal model systems, and to be associated with human dental caries (Refs. 2 through 8) and periodontal disease (Refs. 9 through 12). *Candida albicans* represents a fungus that causes oral yeast infections (Ref. 13).

The Panel considered the inclusion of anaerobic oral pathogenic bacteria, but, because of the technical difficulties involved in their culture (Ref. 14), rejected the choice. The other possible choices of oral representatives included *Veilonella alcalescens,* an anaerobic gram negative oral pathogen that was rejected because it had not been shown to cause oral diseases (Ref. 15). Spirochetes are widely regarded as being involved in periodontal disease, but they would not be suitable test organisms because they cannot be readily cultivated, if at all (Ref. 16). *Bacteroides melaninogenicus* and *Bacteroides asaccharolyticus* have been recently implicated in periodontal disease (Refs. 17 and 18). These species are obligate anaerobes and require careful and complex anaerobic culturing. The use of these two as test organisms would represent an escalation in the cost and time necessary for the in vitro testing of antimicrobials.

In view of the difficulties in cultivating oral anaerobes, the in vitro test was limited to the three test organisms, which at present, are the most odontopathic members of the supragingival plaque. It was suggested in the guidelines that *Pseudomonas aeruginosa* be employed as representative of the gram-negative oral bacteria, should that choice prove desirable (Ref. 19). These recommendations were approved by the Panel.

A recommendation, not approved by the Panel, was that chlorhexidine be used as a positive control. Chlorhexidine is the most effective in vivo plaque agent yet described (Refs. 20 through 23). A minority of the Panel recommended the use of chlorhexidine because evidence was desired that the antimicrobial mouthwashes were bioequivalent to chlorhexidine. Although chlorhexidine is not yet available for use by the public in the United States because of several problems involved with this antimicrobial agent (Ref. 24), it remains the most effective antiplaque agent, one to which all others might ideally be compared.

These guidelines for the in vitro test were suggested as pathways to a scientific evaluation of the antimicrobial activities of oral mouthwashes.

3. *Guidelines for the clinical evaluation of antimicrobial mouthwashes or mouth rinses.* The translation of the evidence obtained by in vitro testing to measure the efficacy in the oral cavity was a challenge. It became apparent to the Panel that progress to the stage of clinical trials was inevitable, given the current data base available in dental research.

The formulation of guidelines acknowledged that dental plaque, for the most part, is a microbial aggregation or clumping of bacteria on the tooth surfaces. Numerous cultural and electron microscopic studies confirm this fact (Refs. 25 through 32). Clinical investigations have demonstrated repeatedly that cessation of oral hygiene in humans results in increases in the amount and extent of dental or bacterial plaque and leads to inflammation of the oral mucosa or gingivitis (Refs. 9, 33, and 34). Once oral hygiene is reinstituted, the amount and extent of dental plaque decrease and the gingival inflammation decreases; moreover it has been demonstrated that mechanical debridement procedures designed to reduce dental plaque are essential for optimal periodontal health (Refs. 35, 36, and 37).

This relationship also existed when chlorhexidine was used as a mouthwash by human volunteers. The use of the antimicrobial mouthwash or dentifrice gel, twice daily, at a concentration of 0.2 percent of chlorhexidine gluconate resulted in a drastic reduction in gingivitis and dental caries (Refs. 38 and 39).

It has also been demonstrated that some of the quarternary ammonium compounds, cetylpyridinium chloride and benzalkonium chloride, if used as a mouthwash show plaque-inhibiting properties approaching that of chlorhexidine (Ref. 40).

This evidence, together with submissions from industry and published papers in the literature, documenting the antiplaque activity of various mouthwashes, make it reasonable to accept that reduction in dental plaque, resulting from daily use of mouthwashes, probably reduces gingival inflammation and possibly may reduce dental caries (Refs. 41 through 49).

The Panel at first accepted this principle and recommended the clinical guidelines for antimicrobial tests based on plaque reduction. The four methods used to grade plaque were:

The Quigley Hein method (Ref. 50) including the Turesky modification (Ref. 51).

The Loe and Silness method (Ref. 52).

The Schick-Ash method (Ref. 53).

The Navy scoring method (Ref. 54).

They were freely accepted by the Panel.

At the 27th meeting, the next to the last meeting, of the Panel on August 14, 1979, the guidelines, previously accepted, were abandoned.

It is the opinion of this minority that a set of guidelines are necessary to determine the effectiveness of a drug. It may have been that the majority of the Panel went too far in trying to formulate an acceptable testing method rather than a set of guidelines. Their reasons for abandonment of these guidelines are not persuasive.

Their reasons are as follows:

The species selected for the in vitro tests were not representative; anaerobes were omitted and a gram-negative bacterium was optimal.

A reduction in dental plaque biomass does not necessarily result in a benefit to the consumer.

A reduction in plaque biomass does not necessarily mean a reduction in plaque bacteria.

Subjective methods of assessment of dental plaque are not valid.

The daily use of oral mouthwashes may cause a shift in the oral flora that may result in a proliferation of pathogenic bacteria.

The minority of the Panel dissents from these five assertions:

As was discussed previously, the oral bacteria species chosen for the in vitro tests were representative of the three leading oral pathogens. (See part IV. paragraph D.2. above—Guidelines to determine the effectiveness of antimicrobial mouthwashes or mouth rinses in the laboratory.) A fourth species, *Pseudomonas aeruginosa* was suggested as an optional representative of the gram-negative bacteria.

It would have been sufficient to select only one test organism to demonstrate antimicrobial activity because bacterial susceptibility differences to antimicrobial chemicals are usually slight. Three test organisms that were selected, the two facultative anaerobic gram-positive bacteria and the fungus, covered most of the susceptibility differences to antimicrobial activity.

As was discussed elsewhere, reduction in plaque biomass in humans who have temporarily abandoned oral hygiene practices results in reduction of gingivitis. (See part IV. paragraph D.3. above—Guidelines for the clinical evaluation of antimicrobial mouthwashes and mouth rinses.) Reduction in plaque then certainly reduces the disease potential by prophylactically reducing the visible periodontal disease, and if the antimicrobial mouthwash can penetrate the gingival crevice, it may reduce the hidden periodontal disease. It most certainly does act prophylactically by reducing the pathogenic challenge to the periodontal tissues by killing a minimum number of oral microorganisms located adjacent to and below the margins of the gingiva.

Tens of millions of United States citizens suffer from one mild form of periodontal disease, namely gingivitis caused by the presence of dental plaque. Most of these individuals are not treated for this disease and only toothbrushing, flossing, and the use of antimicrobial mouthwashes prevent in many of these individuals the extension of the gingivitis to the more severe forms of periodontal disease. The action of the mouthwashes are of short duration but this temporary reduction combined with other oral hygiene techniques benefits the consumer.

This minority of the Panel recommends that those antimicrobial mouthwashes or mouth rinses which have demonstrated the ability to reduce dental plaque and reduce or prevent gingivitis or do both be approved in Category I and be allowed the claim "temporarily reduces gingivitis-causing dental plaque when used together with toothbrushing and flossing."

There are two kinds of measurements that have been used to assay plaque biomass. These are area measurements and plaque weight measurements.

The area measurements, such as the Quigley-Hein system (Ref. 50), is a method for assessing the effectiveness of various procedures in removing dental plaque from different surfaces of the teeth. The individual takes a disclosing rinse or is subjected to a fluorescing light which will disclose

plaque on the tooth surface. The buccal (cheek) or labial (lip) surfaces are inspected and a numerical value is given depending on how much of the tooth surface area is covered by the disclosed plaque. Area measurements are subjective to a degree since they require evaluation by an examiner, and they are somewhat inexact because they may not distinguish between thin films or thick films of dental plaque.

Weight measurements of dental plaque, on the other hand, are useful in determining whether a non-mechanical agent is exerting some effect on the amount of dental plaque during a specific period of time. The method selects certain tooth surfaces and the dental plaque is thoroughly and carefully removed. The plaque is thoroughly and carefully removed. The plaque samples may be placed in preweighed capsules, to minimize water loss, and then weighed. Another method is to weigh the sample immediately; or a third method is to dry the samples, eliminating water content differences, and then weigh the samples. In this manner, the effect of an antimicrobial mouthwash can be analytically and objectively measured and a decrease can be analytically and objectively measured and a decrease in the mass of dental plaque formed during a specific time period quantified.

When weight measurements are done, it has been demonstrated that there is a reduction in the number of plaque bacteria on the tooth surface. Plaque is more than 80 percent bacteria (Ref. 56). A 100-percent reduction in dental plaque on the tooth surface would mean a more than 80-percent reduction in plaque bacteria on the same surface.

One of the bases for the decision of the majority of the Panel that a reduction in plaque biomass does not necessarily reflect a reduction in plaque bacteria was a comment by a consultant to the Panel who said that "it may be possible to reduce biomass without killing plaque bacteria." The consultant failed to indicate that this was a theory that had not yet been demonstrated to function in the human oral cavity. He cited three possible mechanisms for this nonantimicrobial plaque reduction:

Fluoride—Recent evidence suggests that the primary action of fluoride mouth rinses is antimicrobial (Ref. 57).

Phytate—Phytate acts as a chelater, removing calcium from the plaque environment. The consultant was experimenting with phytate at the time, but had not demonstrated that it removed dental plaque in the human oral cavity.

Dextranases—Dextranases are supposed to break up the extracellular glucans which consist of less than 2 percent of the dental plaque. Dextranases have been shown to be ineffective in human clinical trials (Refs. 58, 59, and 60).

There is no evidence to the knowledge of this minority that a nonmechanical agent may reduce dental plaque without reducing plaque bacteria.

There is no justification for the abandonment of the in vivo guidelines, especially since they are guidelines. The present "state of the art" is that area measurements of plaque tend to be somewhat subjective and inexact; while weight measurements are objective and more accurate but tedious. As the "state of the art" progresses there will be less tedious and more accurate methods of plaque assessment. These methods will fall within the spirit of these guidelines. The presently available methods while not ideal are adequate to assay reductions in plaque.

The possibility of a shift of the oral flora with long-term and daily use of an antimicrobial mouthwash does have a scientific basis (Ref. 6). In a year-long study on a small number of humans who used a 0.5-percent chlorhexidine-containing gel dentifrice, there was a reduction in the proportion of the more pathogenic (cariogenic) *Streptococcus mutans* and an increase in the less pathogenic *Streptococcus sanguis* from 0.002 percent of the flora prior to treatment, to 34 percent of the flora after treatment. This shift was beneficial for the subjects. None of the other pathogens, staphylococci, streptococci, gram-negative rods, or yeasts, increased.

There are no reported cases in the literature of pathology as the result of a shift in oral bacteria following daily and long-term use of antimicrobial mouthwashes.

There is as yet no evidence that a shift in oral flora, if it occurs as a result of the long-term use of mouthwashes, will result in a pathological condition in the oral cavity.

4. *Approval of cetylpyridinium chloride, domiphen bromide, and benzethonium chloride as Category I ingredients for safety and effectiveness for use on the oral and pharyngeal mucous membranes.* On August 14, 1979, at the 27th, next to last, meeting of the Panel, the Panel by a vote of four votes approving and two abstaining reversed its previous position (Category I) and changed the categorization of cetylpyridinium chloride, domiphen bromide, and benzethonium chloride from Category I to Category III for both safety and effectiveness for use on the oral and pharyngeal mucous membranes. The majority of the Panel arrived at this decision because their previous vote approving these three as Category I was based on experiments suggested by the in vivo and in vitro guidelines, which the Panel had abandoned. Their concern for safety was based on a lack of long-term studies on the carcinogenicity, teratogenicity, and pathology resulting from a shift in the oral flora. Their loss of faith in the effectiveness of these three ingredients was not as a result of new evidence demonstrating that they were not effective, but rather on their loss of faith, after 4 years, in the in vitro and in vivo guidelines which they previously had approved and then abandoned.

On December 14, 1979, at the 28th meeting, the last meeting of the Panel, a vote was taken on a motion to approve cetylpyridinium chloride, domiphen bromide, and benzethonium chloride as Category I for safety and effectiveness in oral health care for use on the oral and pharyngeal mucous membranes. There were three votes for and four votes against the motion. The following is the minority's point of view.

There have been a number of reports published in the dental literature demonstrating the clinical effectiveness of these three antimicrobial agents in reducing dental plaque (Refs. 41, 42, and 45 through 49). A journal article must undergo review by peers before it is accepted for inclusion in a scientific publication. Publication in the literature indicates scientific approval. The antiplaque claim of cetylpyridinium chloride, domiphen bromide, and benzethonium chloride can be said to be accepted by the scientific community to be effective in reducing bacterial plaque. Bacterial plaque, the scientific community agrees, is the cause of dental caries and one of the possible causes of periodontal disease.

The following is a direct quote from an article by Johnson and Rozanis (Ref. 62):

"Quarternary Ammonium Compounds"

Because the daily use of commercial mouthwashes to 'sweeten one's breath' is a common practice in many parts of the world, their potential as a valuable public health measure in the control of dental disease is enormous. Studies on two commercial brands containing quarternary ammonium compounds have shown some beneficial effects in short-term trials. Cetylpyridinium chloride and domiphen bromide have been studies, and claims of a reduction in plaque and gingival indices have been made. When cetylpyridinium chloride was tested, there was a decrease in plaque accumulation but no significant reduction in the gingival index. Perhaps the lack of gingival effect, despite the reported inhibition of supragingival plaque, is due to the fact that those bacteria effected are not the ones involved in the initiation and

progression of gingivitis or the agents are not carried subgingivally where they can "attack" those bacteria that are possibly more intimately related to the development of the disease.

Gjermo, Baastad, and Rolla (Ref. 48) demonstrated a rather good in vitro inhibition of plaque formation with a 0.2-percent solution of benzalkonium chloride. However, when tested clinically, four of the five volunteers developed painful desquamative lesions of the oral mucosa and the investigators discounted it for general use. Compton and Beagrie (Ref. 49) gained a 42-percent reduction in plaque, but not statistically significant decrease in gingivitis, with benzethonium chloride.

Aside from the elimination of benzalkonium chloride as a safe and effective mouthwash, cetylpyridinium chloride, domiphen bromide, and benzethonium chloride have been shown in the above excerpt to be effective in reducing dental plaque in short-term studies while not necessarily reducing the index of gingival inflammation. Their therapeutic value may be questioned, but their prophylactic effectivity is unquestioned.

These three are effective and should be reinstated in Category I. The minority of the Panel would also suggest that other mouthwashes that meet the criteria of the guidelines be approved as Category I for effectiveness for use on the mucous membranes of the mouth and throat.

5. *Proposal for the antimicrobial evaluation of oral cavity products*—a. *Introduction of the problem.* Standard methods are needed to determine the effectiveness of antimicrobial agents used in the oral cavity. The antimicrobial agents may be natural or synthesized chemical elements, compounds or mixtures of compounds used in antiseptics, disinfectants, astringents, gargles, lozenges, troches, or mouthwashes. The antimicrobial activity is the property of antiseptics or disinfectants to be assayed.

The present method of determining the relative antimicrobial efficiency of any of the chemical disinfectants is to compare them to another disinfectant. One of the official tests used, at present, to compare disinfectants is the phenol coeffficient test. This test is a standardized technique of determining the antimicrobial power of a given chemical compound as compared to that of a standard disinfectant, phenol.

The phenol coefficient of a chemical compound is a numerical value presumed to indicate whether, and to approximately what extent, a chemical compound is a better or poorer compound than phenol. This numerical value is obtained from a ratio of the minimal sterilizing concentration of a given compound as compared to the minimal sterilizing concentration of phenol tested under standard conditions. In the official tests used by FDA and other regulatory agencies of the U.S. government, the following standard procedure is followed. A chemical disinfectant is diluted to given concentrations. The standard disinfectant, phenol, is similarly diluted. A standard concentration of a designated bacterial culture is added. The most dilute concentration capable of killing the bacterial culture after 10 minutes of exposure is the end point for the given chemical disinfectant. Phenol is tested under identical conditions. The end point dilution of phenol is divided into the end point dilution of the given disinfectant and the ratio obtained.

In the official phenol coefficient test, the test bacterial cultures that are commonly employed include *Salmonella typhosa,* a representative of a pathogen of the intestinal tract, and *Staphylococcus aureus,* typical as a major environmental source of wound infection and some spore-forming bacteria. Occasionally, other test organisms are utilized.

The phenol coefficient provides a reasonable index for comparing various phenol derivatives which exhibit kinetics and modes of action similar to phenol. It is less than satisfactory for other antimicrobial agents which may differ in their concentration action curves, temperature coefficients, and their susceptibility to neutralization by their immediate environment. Consequently, many variations of the phenol coefficient test have been developed to evaluate the antimicrobial potency of nonphenolic compounds. These variations depend upon a sterility end point.

Microbiologists agree that this end point of sterility is questionable and a more accurate assay of antimicrobial activity would be on the rate of killing of bacteria by the chemical. The rate of killing or reaction velocity constant is exponentially related to the concentration of the disinfectants according to the following expression: $K=C^nt$, where K = the reaction velocity constant of killing, C = the concentration of the chemical, n = a constant characteristic for each chemical, and t = the time of contact.

It would be difficult technically to determine the rate or kinetics of killing; as a result, the tests utilizing the less accurate and less precise sterility end point are more commonly employed.

Generally, assays for the effectiveness of antimicrobials are made by testing known concentrations of antiseptics or disinfectants against one or more test microorganisms and comparing it to a standard or control.

b. *Proposal for an in vitro evaluation of antiseptics or disinfectants used in the oral cavity.* Two factors are necessary for the in vitro assay of the antimicrobial or disinfectants, and these are typical test microorganisms and a standard disinfectant.

(1) *Test microorganisms.* Those microorganisms known to cause disease in the oral cavity should be used as test cultures to assay the potency of oral products.

The following strains are suggested as test microorganisms:

(a) *Streptococcus mutans* is one of the gram-positive cocci microorganisms implicated in the development of dental caries. It has been directly associated with active carious lesions and in the formation of dental plaque. It is typical of the other oral streptococci. Presumably, any disinfectant that kills *Streptococcus mutans* would be equally effective against any of the other oral streptococci.

(b) *Actinomyces viscosus* is a gram-positive filamentous rod recently implicated in the triggering of experimental periodontal disease. This bacterium is typical of the filamentous bacilli found in dental plaque. If an oral product has any therapeutic value, it should inhibit this class of oral microorganism.

(c) *Candida albicans* is a yeast found in the oral cavity. It may be more difficult to inhibit than *Streptococcus mutans* or *Actinomyces viscosus.* It is involved in oral yeast infection including denture sore mouth. This organism is typical of the oral fungi.

Other test organisms may be employed as it becomes appropriate. Gram-negative bacteria constitute a minority of the oral flora, and most are anaerobes which present technical problems in cultivation. Gram-positive bacteria and yeasts present greater challenges to disinfectants than do the gram-negative bacteria.

Viruses must be cultured in cells in tissue culture and present a greater laboratory hazard and technical difficulties. Once the hepatitis virus B (Dane particle) is routinely cultured, it could be used by virucidal testing.

(2) *Standard disinfectant or antiseptic.* Ideally, a proven effective disinfectant should be used as the standard. At present, there appears to be only one compound that will inactivate *Streptococcus mutans* and other caries-inducing experimental caries, and retard or reverse incipient

periodontal disease. This disinfectant is chlorhexidine, an antibacterial bisbiguanide. Its chemical name is 1,6-*DL*-(4-chlorophenyldiguanido) hexane. It has a large antimicrobial range against a wide range of bacteria. It is being used in Europe as a topical antiseptic and as a disinfectant in genitourinary diseases as well as diseases of the eye and oral cavity. It is a potent antibacterial commercially available in Europe as the gluconate or acetate salt.

Chlorhexidine is also antimicrobial to other oral streptococci, *Staphylococcus arueus, Escherichia coli,* and *Candida albicans.* It is inhibitory to a wide variety of microorganisms, but is not sporocidal, except at temperatures approaching the boiling point of water. Viruses do not appear to be susceptible to the action of chlorhexidine.

The possible mode of action of chlorhexidine is to exert a lethal action on the cell surface of microbial cells by disorganizing permeability barriers and coagulating the cytoplasmic contents.

This disinfectant, chlorhexidine, would be an ideal standard. It is effective at 1 to 2 percent dilutions and will inhibit the three proposed test organisms: *Streptococcus mutans, Actinomyces viscosus,* and *Candida albicans.*

The chlorhexidine "coefficient test" would be used to compare any oral product against chlorhexidine. The ratio obtained would demonstrate the relative efficiency of a product as compared to chlorhexidine.

c. *Proposal for the in vivo evaluation of antiseptics or disinfectants used in the oral cavity.* An in vivo method should measure parameters that will result in improved oral health.

Three parameters are used at present:

(1) Reduction in the quantity of dental plaque.

(2) Reduction in the numbers or kinds of microorganisms in the saliva.

(3) Reduction in the numbers or kinds of microorganisms in dental plaque.

The reduction in the quantity of dental plaque is determined by the use of disclosing agents or stains. The teeth are stained with dyes, or chemical disclosing agents, and examined under white light or ultra-violet light. Photographs are taken, and the areas colored by the light or the stain are mapped, measured, and compared to the total area of the teeth. This procedure is used before and after the use of a disinfectant.

The defects in this method are that it is laborious, tedious, and difficult to reproduce. It is time consuming, but its greatest defect is that it is inaccurate.

The reduction in the number or kinds of microorganisms in saliva is another measurement of the efficacy of oral disinfectants. Saliva is only one of the sites of the microbial flora.

The late Dr. Henry Scherp compared this method to a determination of the bacterial content of the soil at the headwater of the Mississippi in Minnesota by measuring the river water at New Orleans. It does not accurately describe what is occurring on the tooth surface nor in the gingival sulcus areas where most dental disease occurs.

A more accurate general in vivo method that reflects microbial changes on the tooth surface or in the gingival sulcus is one in which plaque material is quantified for reduction in the plaque flora.

Plaque is removed from designated areas on the tooth surface or gingival crevice. It is weighed to obtain a value per milligram of plaque. It is sonicated carefully to disperse the plaque. Isolated species may be identified and quantified, or groups may be quantified. In this manner reductions in microbial counts in areas important in dental disease can be determined.

There are many variations on this in vivo technique. One such variation developed which has been used to quantify microbial reduction on the tooth surfaces by mouthwashes is the agar replica method.

In the agar replica method, an impression of the patient's teeth is taken before and after use of the mouthwash in irreversible hydrocolloid. The bacteria on the surface of the plaque are transferred to the impression material. Bacterial culture medium is poured aseptically into the hydrocolloid impression. The bacteria are transferred from the impression material to the surface of the agar. The agar shrinks slightly and is removed from the impression. A model of the patient's teeth and gingiva are obtained with colonies of bacteria growing in the exact sites they occur in the mouth. These colonies are counted after incubation and by comparing the before and after use of the mouthwash, one can quantify the reduction in microorganisms colonizing the tooth surface or upper portion of gingival sulcus.

One of these in vivo methods should be adopted, as is appropriate, to measure the antimicrobial activity of oral cavity products. This minority of the Panel suggests it be either the direct sampling from plaque and counting microorganisms or one of the variations such as the agar replica technique.

In summary, this minority of the Panel makes the following recommendations:

It is recommended that an in vitro test utilizing chlorhexidine, an effective oral disinfectant, as a standard be used and all other oral products be compared to this standard. This will serve to give an estimate of relative antimicrobial potency of oral products.

In the above test, three easily cultivable and identifiable oral organisms, *Streptococcus mutans, Antinomyces viscosus,* and *Candida albicans,* can be used as test organisms in the in vitro test.

It is recommended that, once an oral product shows promise for relative antimicrobial activity in the in vitro test, it be tested by an in vivo method. A direct sampling of dental plaque from designated areas on the tooth and gingival sulcus or one of its variations should be used.

These two approaches will make possible an accurate evaluation of the antimicrobial properties of oral products.

6. *Additional methodology for evaluating antimicrobial active ingredients*—a. *Introduction.* The objective of this report is to present a protocol of test methods which will determine the effectiveness of antimicrobial agents used in the oral cavity. These antimicrobials are antiseptics, disinfectants, astringents, gargles, lozenges, troches, or mouthwashes which are presently being sold without prescription (OTC) for use by the general public in the oral cavity. The property of these products to be evaluated in this report is their relative antimicrobial activity.

The variety of antimicrobial agents recommended for use in the oral cavity is great. No single bacteriological test method for evaluating all agents can be expected to be adequate for all. The problem of testing these agents should be resolved with the following considerations:

(1) The development of a method which will provide meaningful results.

(2) The precise application of this method.

(3) The accurate interpretation of the results based on adequate controls and a precision sufficiently accurate so that the results can be reproduced uniformly.

b. *Definitions*—(1) *Antimicrobial.* Any physical agent or chemical that destroys or inhibits the growth of any microorganism or virus.

(2) *Antiseptic.* A substance that opposes sepsis, putrefaction, or decay by inhibiting the growth or action of microorganisms or viruses or destroying them. This term is used especially for agents applied to living tissue. Mouthwashes or gargles can be called antiseptics only if they destroy microorganisms during their period of

contact in the dilutions recommended for use.

(3) *Disinfectant.* An agent that frees from infection. It is usually a chemical agent which destroys harmful microorganisms or viruses, but not usually bacterial spores.

(4) *Germicide.* A term used interchangeably with "antiseptic" or "disinfectant" but one that implies that all vegetative (non-sporing) microorganisms are destroyed.

c. *Methods*—(1) *In vitro evaluation of antiseptics or disinfectants used in the oral cavity.* Oral antiseptics or disinfectants which are applied for a short time as in gargles, sprays, or mouthwashes are tested by the following methods:

(i) *Test organism. Streptococcus mutans,* strain NCTC 10449.

(*a*) *Medium.* Calf brains, infusion from, 200 g; beef heart, infusion from, 250 g; proteose peptone, 10 g; bacto-dextrose, 2 g; sodium chloride, 5 g; disodium phosphate, 2.5 g.

This medium is brain heart infusion broth (BHI). Thirty-seven grams of the BHI is dissolved in 1,000 mL distilled water. Ten milliters of BHI broth is added to 20 x 150 mm unlipped test tubes, plugged with cotton and sterilized in the autoclave in 15 pounds per square inch ($lb/in^2$) pressure at 121° C for 30 minutes. The final reaction of the medium will be pH 7.4.

(*b*) *Stock culture.* Each stock culture of *Streptococcus mutans* is transferred on agar slants of BHI twice a month and stored at refrigerator temperatures.

(*c*) *Test culture.* The test culture is prepared by transferring from the agar slant stock culture into 10 mL of the above broth medium and transferred and incubated at 37° C for 16 to 18 hours. This is done for 3 consecutive days to prepare the test culture.

(*d*) *Medication tube.* Unlipped test tubes 25 x 150 mm plugged with cotton and sterilized in the hot air oven at 170° C for 1.5 hours are used for mixing the cultures with the antiseptic or disinfectant in the test.

(*e*) *Temperature of the test.* The antiseptic and the test culture must be warmed in a warm bath at 37° C and held at this temperature during the period of the test.

(*f*) *Inoculation loop.* A 4-mm loop of platinum wire U.S. No. 23B and S gauge, 0.5 to 3 in long set in a suitable holder such as an aluminum or glass rod 0.5 cm in diameter is used to transfer the antiseptic culture mixture in a medication tube to 10 mL of the sterile broth in the subculture tubes. The loop and rod are flamed before each transfer which is made under aseptic conditions.

(*g*) *Incubation.* The subcultures are incubated at 37° C for 48 hours.

(*h*) *Dilution.* Any series of dilutions which may be required are made in sterile distilled water under aseptic conditions or the antiseptic may be tested at the dilution suggested by the manufacturers.

(*i*) *Methods of conducting tests.* Five milliliters of the antiseptic in the appropriate dilution is placed into sterile 25 x 150 mm tubes and warmed to 37° C in a water bath. The 16–18 broth culture of the test organism (and culture) after vigorous shaking is allowed to warm in the same water bath for 5 minutes. Five-tenths milliliters of this culture is removed by the means of a 1 mL graduated pipet and added to 5 mL of the antiseptic and mixed by slight agitation. Transfers are then made from the mixture of culture and antiseptic into 10 mL of sterile broth by the means of the sterile 4-mm loop at intervals of 30 seconds, 1, 2, and 5 minutes. These transfer tubes are then incubated at 37° C for 48 hours. At the end of the incubation period, these broth tubes are observed for evidence of growth.

The information desired from this method is the concentration of the germicide required to kill *Streptococcus mutans* under the conditions of the test within 5 minutes as compared to a standard or control agent. This agent is chlorhexidine, a compound shown to be effective against plaque bacteria. If the preparation does not kill without any comparison within 5 minutes, it has been considered not sufficiently germicidal to be classified as an antiseptic for use in the oral cavity.

Those preparations that do pass this test within 5 minutes can be then compared to chlorhexidine for their relative efficiency. In this test, 1 percent chlorhexidine is the germicide which is commonly considered to have some antiseptic clinical value to oral microorganisms to kill within 5 minutes. In the interest of fairness, if the concentration suggested by the manufacturer of the disinfectant is below or above 1 percent, it may be suitable to employ the same concentration of chlorhexidine as the recommended concentration of the antiseptic. For example, if an antiseptic is to be used at 0.5 percent, then chlorhexidine would be diluted to a 0.5-percent concentration. If the antiseptic failed to kill the test organism at 0.5 percent, but did kill at 2 percent, it would be judged to be 25 percent as effective as chlorhexidine.

The principal value of this method would seem to be that of determining the relative germicidal levels of oral antiseptics and disinfectants intended to provide contact germicidal action.

(ii) *Confirming tests.* There is always the possibility that enough of the germicide may be carried over into the subculture broth to inhibit the growth of test organisms, and false negative results may often occur. For this reason, it is necessary to determine whether the inhibitory concentration of the germicide is present in the broth.

The subculture is made by reinoculating these tubes into fresh 24-hour broth culture of the test organism by means of a sterile loop and reincubating at 37° C for 24 hours. If growth occurs after this inoculation, it means that no inhibitory action has occurred and that failure of growth during the first incubation shows that the test organisms have been killed. In case no growth occurred after the second inoculation, the test is repeated using 250 mL of broth in a flask in place of the 10 mL to avoid inhibitory reaction of the antiseptic to the subculture.

It may be that this germicidal action of the oral antiseptic would not be the same in applications in vivo as mouthwashes and gargles where the concentration would be reduced in actual application by the saliva and other body secretions, and the active ingredient would be exposed to the potentially inactivating effects of those same secretions. The details of the procedures here are, however, sufficiently flexible so that application dilutions and organic inactivating materials can be simulated with some degree of success. It is, therefore, suggested that if an oral germicide passes this stringent test, it should be tested in the presence of human saliva before it can be recommended in the oral cavity.

(iii) *Tests in the presence of saliva.* One milliliter of whole human saliva that has been sterilized by filtration through a membrane filter (e.g., Millipore) with a diameter of 0.45 mm is added to the modified test described above. This gives an equivalent further dilution of the antiseptic or disinfectant as well as the control disinfectant (chlorhexidine). In this manner a germicide can be screened for oral use (with saliva) for use as a mouthwash or gargle.

(*a*) *Test organism. Actinomyces viscosus,* strain ATCC 19246.

The same procedures as followed with *Streptococcus mutans* will be followed with *Actinomyces viscosus* except that 24-hour cultures of test organisms are used.

(b) *Test organism. Candida albicans,* strain ATTCC 18804.

The same procedures are followed except the culture media for this yeast is malt extract broth. Fifteen grams of Bacto-male extract broth is dissolved in 1,000 mL of distilled water. This medium is placed in tubes as described above and autoclaved for 15 minutes at 15 lb/in$^2$ pressure at 121° C. The final reaction of this medium will be pH 4.7. This medium is used in place of the BHI for the propagation of the test yeast. A 24-hour culture of this yeast is preferred to test the fungicidal action of the germicide. The tests are conducted as above.

(iv) *Gram-negative testing.* If it is necessary to test a gram-negative organism, then *pseudomonas aeruginosa,* strain ATCC 10145, is used. The above procedures are followed except culture medium.

*Medium.* Beef extract 5 g, peptone 10 g, sodium chloride 5 g are added to 1,000 mL of distilled water. Boil for 30 minutes to dissolve, adjust the pH to 6.8 with normal sodium hydroxide or saturated aqueous sodium carbonate ($Na_2CO_3$). Boil for 10 mnutes and then filter through paper and make up to original volume. Add 10 mL to the 20 x 150 mm unlipped test tubes, plug with cotton and sterilize in an autoclave at 15 .b/in$^2$ pressure at 121° C for 30 minutes. This is nutrient broth and can be purchased as nutrient broth. The final pH should be adjusted to 7.4. The same procedure as described above is used for this with 24-hour cultures of the test organism.

(v) *Summary of in vitro tests.* (*a*) Modified chlorhexidine coefficient tests using three test cultures.

(*1*) *Streptococcus mutans.*

(*2*) *Actinomyces viscosus.*

(*3*) *Candida albicans.*

(*4*) If necessary, *Pseudomonas aeroginosa.*

(*b*) Subcultures of above.

(*c*) Modified chlorhexidine coefficient test with 1 mL of sterile saliva.

(2) *In vivo evaluation of oral antiseptica and disinfectants*—(i) *Indroduction.* The efficacy of an oral antiseptic or mouthwash can be best evaluated by its ability to kill microorganisms in the oral cavity. As mentioned in the original proposal, the reduction in number of microorganisms in dental plaque per given weight of dental plaque seems to be the most accurate method to describe the germicidal properties of agents in the oral cavity. Killing of microorganisms. in saliva is inaccurate, and the germidical action on soft tissue is inconsistent. Two methods are proposed:

(*a*) *The reduction of microorganisms in plaque on disignated tooth surfaces in human volunteers.* Plaque is removed from designated areas on the tooth surface or gingival crevice. Prior to the use of the antiseptic, this may be done on every other tooth. For example, it maybe the facial area of the right central incisor, the buccal area of the right canine, the buccal area of the second premolar, and buccal area of the second molar together with a sampling from the corresponding gingival crevises. The plaque can be removed with a standard periodontal spoon, and the plaque is immediately placed in a preweighted gelatin capsule. Immediately after collection, the capsule is weighed and amount of plaque calculated. The capsule and its contents are aseptically homogenized in 5 mL of trypticase-soy broth. One milliliter of the homogenized plaque material is then added to 9 mL of sterile phosphate buffer. The dilution is mixed, and 1 mL of this dilution is then transferred to a second tube containing 9 mL of phosphate buffer (pH 6.8). This is continued for 8 more tubes until a dilution of $10^{10}$ is obtained.

One milliliter of each dilution is then placed in sterile standard petri dishes. This is done in triplicate so there are three petri dishes each containing 1 mL of each dilution. Over this dilution in each tube is poured 20 mL of tripticase-soy agar which has been melted and cooled to 45° C. The petri dishes are gently agitated in order to achieve a homogenous mix. These are appropriately labeled and then incubated for 48 hours in an inverted position at 37° C.

After incubation the plates are removed and the number of colonies on each plate counted. Any appropriate counting method may be used. Only those plates having between 30 and 300 colonies are counted, and the number of microorganisms per milligram of plaque is calculated. For example, if 10 mg of plaque were collected and then diluted completely, the number of milligrams per 20 mL culture medium means there was 0.5 mg per mL. The number of microbial colonies, for examplke, at the $10^6$ dilution may be 40. This means that there were $80 \times 10^6$ (80,000,000) microorganisms per milligram of plaque.

The human volunteer then uses the mouthwash, gargle, or other oral antiseptic as directed by the manufacturer. The mouth is rinsed with sterile saline to remove all traces of residual antiseptic. Then plaque is collected from those teeth in the same quadrant that were not sampled before use of the mouthwash. The right lateral, first premolar, first molar and third molar may be sampled. The sample of collected plaque again is weighed and diluted as described above. The dilutions are plated and counted. For example, if now there are only $40 \times 10^5$ microorganisms per milligram (4,000,000) of plaque, then a reduction of $76 \times 10^6$ (76,000,000) was obtained by use of the mouthwash.

If a relative efficiency is necessary, then the same dilution of chlorhexidine could be tested in human volunteers against the mouthwash, and the relative efficiency could be determined using the above method simply by comparing the numbers reduced by the antiseptic against the control chlorhexidine.

The method described above is tedious, but new methods have been developed to do this rapidly, and instrumentation using laser counting has been developed in order to rapidly count colonies on the bacterial plates. This method is tedious, but would give an accurate general in vivo method that will reflect changes on the tooth surface or in the gingival crevice.

The methods for counting bacteria in the plates are varied. They can range from counting on a Quebec Colony Counter manually to the various mechanical counters available in microbiological laboratories.

(*b*) *Agar replica method.* The principle of the agar replia method is that microorganisms on the surface of teeth in plaque can be transferred to the surface of a dental impression material taken of the entire dentition. The next step is to pour up dental impression bacteriological agar culture media. The bacteria are now transferred to the surface of the agar model. The agar model is incubated, and the microbial colonies can be seen growing in the exact site that they occur in the mouth.

The patient rinses his/her mouth with sterile distilled water. A dental impression is taken in irreversible hydrocolloid. Perforated impression trays are used and Jeltrate®, an irreversible hydrocolloid containing little fluoride, is used as the impression material. It is mixed up, the surface of the material is washed, it is placed over the patient's teeth, and an impression is obtained of the patient's teeth. The impression material is carefully placed and removed so that a minimum streaking of dental plaque would occur.

The impression are boxed in wax and immediately poured with a fortified selective agar medium. The medium is melted and then cooled to 47° C so that it would solidify on contact with the hydrocolloid. The poured impressions are chilled, adn the agar medium model is carefully removed from the impression material.

At present two selected media have been used. The first is a modification of the formula of Rogosa, Mitchell, and Wiseman (Ref. 63). It consists of a

lactobacillus-selective broth containing brom cresol green, .02 g/L and 3 percent fortified agar (Ion agar #2). The pH of the media is adjusted to 5.5 with lactic acid. Agar models obtained using this impression are incubated anaerobically at 37° C for 48 hours.

A second selective media used for the isolation of oral yeasts is Sabouraud's dextrose broth containing penicillin, 20 units per mL; cyclohexamide, 0.5 mg/ml; streptomycin, 40 mg/mL; and 3 percent fortified agar. Agar models utilizing this media were incubated aerobically at 30° C for at least 72 hours.

These two media select only the lactobacillus in the first or the yeast in the second. As other selective media begin to be developed, they can be utilized to identify certain microorganisms. If total counts are desired, then media such as trypticase-soy or blood agar can be utilized to obtain those microorganisms which will grow on this media.

Agar models are obtained before the use of the mouthwash as described. The mouthwash is then used as recommended by the manufacturer, and models are taken again a second time. Colonies are then mapped on both models at the site. A disappearance of a colony from a certain site can be the result of the use of the mouthwash. The number of colonies that disappear will give evidence of the efficacy of the mouthwash in removing those microorganisms that are chosen by the experimenter. In this way the action on specific microorganisms, or, in the case of the blood agar medium, total microorganisms, can be determined, although not as accurately as the first method.

If a relative effectiveness is desired, again the concentration of the antiseptic to be tested can be compared to the same concentration of chlorhexidine, and a relative efficiency of killing as demonstrated by the agar replica method can be obtained.

d. *Discussion.* Two methods of evaluating the efficiency in vivo of the action of mouthwashes, gargles, and other oral antiseptics have been described. These are two suggested methods and are probably the best ways to obtain information as to the relative efficiency of the oral antiseptics in killing microorganisms in the mouth. Other methods such as saliva counts and scraping of the buccal tissue are less satisfactory and give less accurate and inconsistent evaluation. It should be noted that these are protocols of methods to be used and merely demonstrate the principles that counts in plaque are to be reduced by the antiseptic, and these are two methods suggested.

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## V. Astringents

### *A. General Discussion*

1. *General comments.* An astringent is a substance capable of precipitating albumins and other proteins when applied topically to living cells of the mucous membranes and other tissues.

a. *Mode of action.* Astringents precipitate proteins. They form a thin protective film on the surface of the body cells. This film lessens their sensitivity to external stimuli, such as those of mechanical origin, those due to abrupt temperature changes, and those induced by chemicals. The action on an astringent is essentially limited to the cell surface. The permeability of the cell membrane is reduced, but the cells remain viable and uninjured unless high concentrations or excessive quantities are used, in which case the cell body is affected.

b. *Types and uses of astringents.* Various nontoxic metallic ions and certain organic acids can act as astringents. Derivatives of polyhydroxybenzoic acid, tannic acid, or similar protein-coagulating acids, will precipitate albumins and other proteins. Dilute aqueous solutions of aluminum and zinc salts are commonly used as astringents. Astringents have been alleged to promote healing of superficial lesions by acting as protective agents. Actually, there is no evidence that they promote the proliferation of epithelial or other type of cells and accelerate healing. Astringents merely provide symptomatic relief and are not curative.

Astringents are generally used in the mouth and throat to provide a protective coat over ulcerations, erosions, or abrasions of the mucosa, or over irritated or inflamed surfaces. Astringents are usually used in the form of dilute aqueous solutions. Concentrated solutions may be caustic and penetrate and precipitate the proteins in the interior of the cells, thus causing further injury, irritation, or ulceration. The protective coating often relieves various types of discomfort such as burning sensations, aches, or pains by diminishing or temporarily preventing access of offending stimuli to an irritated or injured surface. They do not possess analgesic activity nor do they depress receptors for pain as do anesthetics and analgesics.

c. *Adverse effects of astringents.* Since astringents are water soluble, they may be absorbed from the mucous membranes and produce systemic effects that are undesirable. Astringents containing tannic acid have caused adverse systemic effects such as liver injury, following absorption. The excessive and repeated use of solutions of metallic ions, e.g., iron and chromium, likewise, has resulted in absorption, causing adverse systemic effects. Use of concentrated solutions may cause irreversible injury to the cells; necrosis and sloughing occur. Some astringents possess varying degrees of antimicrobial activity due to their protein-coagulating properties. The protein-coagulating activity may be enhanced to an undesirable degree when certain antimicrobial agents are combined with astringents.

### *B. Categorization of Data*

1. *Category I conditions under which astringents for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.*

The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

**Category I Active Ingredients**

Alum
Zinc chloride

a. *Alum.* The Panel concludes that alum is safe and effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Preparations of aluminum are widely used in medicine as antacids, antiseptics, and astringents. Aluminum solutions precipitate proteins in the same manner as do solutions of salts of many other metals. Dilute solutions of aluminum salts have an astringent action and are not irritating to the mucous membranes. More concentrated solutions act as irritants and may injure tissues. Insoluble preparations are used as antacids and adsorbents. The chief soluble preparation of aluminum used in medicine is alum or potassium aluminum sulfate ($KA1(SO_4)_2.10H_2O$). The insoluble aluminum hydroxides and phosphates are used as antacids. The acetate and chloride salts are water-soluble salts and are used as antiseptics and antiperspirants. They may also be used as astringents but are more irritating than the alums. Besides the potassium atom, the ammonium complex or sodium atom may be substituted for the potassium atom in the alum molecule. Thus, there are three types of alum-potassium, sodium, and ammonium—all with the same therapeutic effect, but with minor variations in solubilities and chemical properties. The potassium alum is the most commonly used derivative.

Potassium alum is also known as kalinite (Ref. 1). The technical product is also known as alum flour, alum meal, and cube alum. Alum is composed of colorless, odorless, hard, large transparent crystals. It has a sweetish astringent taste. Alum is stable at ordinary temperatures. It is generally available as the decahydrate, which becomes anhydrous above 200° C. One gram dissolves in 7.2 mL water, 0.3 mL boiling water, and is freely soluble in glycerol. Alum is insoluble in alcohol (Ref. 1). The aqueous solution is acidic (pH of 0.2 molar alum is 3.3). Anhydrous alum is sometimes called burnt or desiccated alum, and it attracts moisture from the air. The dodecahydrate is used for medicinal purposes.

(1) *Safety.* The Panel concludes that potassium alum is safe as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Small quantities of aluminum solutions induce no symptoms except a feeling of dryness and "astringency" (puckering) of the mucous membranes of the mouth and throat. Larger doses ingested orally pass into the stomach where they may act as gastric irritants and cause nausea and vomiting and, in extreme cases, exert a purgative effect (Ref. 2). Even when excessive quantities are ingested, no symptoms except those of gastrointestinal irritation and inflammation ensue. The continued use of alum does not result in any symptoms or result in chronic poisoning. Aluminum slats are absorbed only in small quantities from the stomach and intestine. Once they are absorbed, they are stored in the liver, kidney, muscles, and pancreas and slowly excreted into the bile and urine (Ref. 2).

Alum has been and is still used extensively in baking powders. It is estimated that in any ordinary diet seldom more than 60 mg aluminum is ingested per day. This quantity appears to be quite innocuous. Extremely large quantities of aluminum salts taken experimentally or with foods in the form of baking powders have produced diarrhea. No other adverse effects or symptoms of general poisoning have resulted from the ordinary use of such powders. The administration of large quantities of insoluble aluminum preparations to animals and man for use as antacids over long periods of time has produced no obvious symptoms of poisoning. Deaths from the ingestion of toxic doses are rare and attributable to the irritating action on the mucosa of the gastrointestinal tract.

Rats fed 2 mg alum daily did not show diminished growth or fertility or any other damage, even when these experiments were carried out for four generations (Ref. 2).

Practically no absorption occurs when insoluble aluminum-containing compounds are administered by mouth. The soluble salts and the insoluble derivatives that are solubilized by the acid in the stomach such as the hydroxide or the carbonate are absorbed, however. The entire amount of an insoluble aluminate is virtually recovered from the feces and only traces from the urine. When aluminum salt solutions are injected parenterally, they are excreted largely into the urine by the kidney. Some are excreted into the gastrointestinal tract. Organic derivatives of aluminum are used for human therapeutics, as for example, aluminum aspirin which is safe and effective.

(2) *Effectiveness.* The Panel concludes that alum is effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage section below.

The soluble salts of aluminum precipitate proteins. In view of this effect, they are astringent, styptic, and antiseptic in proper dosage. They are not corrosive to intact skin or mucous membranes of the mouth and throat. A 1-percent solution of aluminum acetate precipitates protein and most colloidal suspensions. This property is often employed for clarifying turbid water. The protein-precipitating properties are also used in the purification of toxins and antitoxins. The precipitated protein tends to redissolve in the presence of an excess protein. The precipitation of gelatin or serum proteins is maximal with 8 percent aluminum acetate. This concentration produces maximal contraction of excised rat tendon.

A 1-percent solution of aluminum acetate has been reported to be antiseptic, but the Panel does not regard this as an important therapeutic attribute of soluble aluminum salts. A 5-percent solution is germicidal. A saturated solution of potassium alum in 50 percent alcohol is employed for the prevention of bedsores (Ref. 3).

A 2-percent solution of potassium alum is used topically to suppress excessive sweating by hardening the skin. Aluminum chloride, which is more irritating than the other soluble salts since it is acidic in reaction, is sometimes used as a deodorant and to inhibit localized sweating of the feet and axilla (underarm) (Ref. 4). At first a 25-percent solution is applied twice a week and then later once a week.

Dilute solutions of potassium alum are effective astringents when applied to the mucous membranes of the oral cavity. They aid in the relief of sore throat or sore mouth or both by providing a protective coagulum over irritated or ulcerated surfaces. The relief is merely symtomatic and not due to any curative effect.

Alum is applied on the mucous membranes as an astringent in solutions of 0.5 to 1 percent. A 0.5- to 5-percent solution (Ref. 3) has been used for gargling, but is somewhat irritating and damaging to the teeth and is not recommended by the Panel.

(3) *Dosage.* Adults and children 3 years of age or older: Use a 0.2- to 0.5-percent concentration of alum in aqueous solution in the form of a rinse, gargle, spray, or by swabbing the affected area, not more than three to four times daily. For children under 3

years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care astringent active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 49, 1976.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, PA, pp. 1282–1285, 1957.

(3) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, PA, pp. 48–49, 1973.

(4) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, NY, pp. 949–950, 1975.

b. *Zinc chloride.* The Panel concludes that zinc chloride is safe and effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Zinc chloride may be prepared by reacting metallic zinc with hydrochloric acid (Ref. 1). It may be molded into a pencil form. Since zinc is amphoteric, it is capable of forming acidic and basic compounds. If sodium hydroxide is added to a solution of zinc chloride, sodium zincate forms. In aqueous solution, the sodium zincate ionizes into a sodium cation and a $ZnO_3$ anion. Zinc chloride solution is acidic in reaction; the zincate is alkaline. Zinc salts are not compatible with alkalies and carbonates.

Zinc chloride, sometimes called "butter of zinc," is a white powder composed of deliquescent granules or fused pieces of rods. The solubility of zinc chloride in water is 432 g per 100 g at 25° C. It is soluble in 1.3 mL alcohol and 2 mL glycerol and is freely soluble in acetone. The aqueous solution is acidic on reaction (pH 4) (Ref. 1).

Solutions in water or in alcohol are generally slightly turbid, due to the presence of zinc oxychloride. Zinc chloride has been used as an astringent in mouthwashes in concentrations of approximately 1 percent. Pencils of zinc chloride and alcohol solutions containing up to 30 percent of the salt have been used for their caustic effects (Refs. 2, 3, and 4). Zinc chloride has been used in 0.5 percent concentrations as a vaginal douche for the treatment of *Trichomonas vaginalis* and also for the treatment of leukorrhea.

Numerous other preparations of zinc have been used for medicinal purposes. These may be divided into the soluble compounds such as the chloride, sulfate, or acetate, and insoluble compounds, such as the oxide, stearate, and carbonate, preparations. The insoluble preparations are used topically on the skin. Soluble preparations are used as astringents and for disinfection (Refs. 1 through 4).

(1) *Safety.* The Panel concludes that zinc chloride is safe as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Zinc is found in traces in foods and is indispensable in nutrition. Deficiencies of zinc ion in the diet may cause growth retardation, hypogonadism, skin changes, mental lethargy, and delayed wound healing. The major function of zinc in metabolism appears to be enzymatic. Zinc has been used as an antisickling agent in sickle cell disease. Zinc competes with cadmium, copper, lead, iron, and calcium for similar binding sites (Ref. 5). Various salts of zinc, such as the chloride, stearate, and sulfate, as well as the oxides, have been used externally and internally for the treatment of various dermatological conditions and inflammatory lesions of the mucous membranes of the mouth and throat (Refs. 3 and 4). Zinc sulfate has been used as an ophthalmic astringent solution at a concentration of 0.25 percent.

When taken internally, zinc salts irritate the gastric mucosa; for this reason zinc sulfate has sometimes been used internally as an emetic. It was once considered to be one of the most effective emetic agents for the treatment of poisoning, but it is not used in present day practices.

The intravenous lethal dose in rats in 60 to 90 mg/kg of zinc in a soluble salt. The lethal dose of zinc sulfate is estimated to be in the order of 15 g (Refs. 3 and 4). The oral toxicity of zinc compounds in man is low. Zinc compounds in quantities that might exceed the amount introduced in food, such as from zinc containers, appear to be innocuous. Zinc compounds caused no apparent symptoms or pathologic changes when administered daily for a year to dogs, cats, or rats. In some studies, no symptoms were noted when zinc compounds has been administered for a lifetime to several generations of animals. The zinc contents of the organs was not increased.

Systemic effects of intravenous injection of soluble zinc salts in man are mainly neurologic. Consciousness is lost without involvement of the motor areas. However, the subject is areflexic due to the comatose state. The blood pressure falls rapidly, probably as a result of the flocculation of plasma protein. Blood coagulation is retarded for approximately an hour after the injection of 5 to 50 mg/kg in rabbits, probably caused by a decrease in antithrombin. Long, continuous injection of zinc salts by catheter results in fibrotic changes in the acinar portion of the pancreas without affecting the islets. Chronic industrial zinc poisoning has been reported in workers in galvanizing plants. The symptoms in man are chiefly gastrointestinal (nausea and vomiting). Hypochromic anemia may also occur. Feeding zinc to rats produces hypochromic anemia and deficiency in growth (Ref. 4).

Inhalation of fumes of zinc oxide causes "metal fume fever." This is an industrial hazard noted among workers in plants where metallic zinc is heated. The zinc oxide is formed due to the oxidation of the metal. Inhalation of powdered zinc stearate produces the same symptoms. Presumably the crystals cause a temporary, reversible change in the epithelium of the respiratory tract.

Nasal sprays of zinc sulfate have been used to shrink the mucous membranes to allow drainage from infected accessory nasal sinuses. This type of treatment has the disadvantage in that it inhibits the activity of the cilia of the mucous membranes of the respiratory tract and favors the retention of secretions. Such decreased activity can also occur when these agents are applied to the mucous membranes of the oral cavity (Ref. 3).

(2) *Effectiveness.* The Panel concludes that zinc chloride is effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The salts of zinc are employed as astringents, corrosives, and mild antiseptics. They, most likely, owe their astringent effects to the ability of the zinc ion to precipitate protein. Soluble salts of zinc usually are almost completely ionized. Dilute solutions of zinc chloride and zinc sulfate are effective astringents. In high concentrations they are irritating to mucous membranes. The insoluble compounds, such as the oxide, or stearate, are used externally and are not irritating (calamine).

Dilute solutions of zinc chloride are effective astringents when applied to the mucous membranes of the mouth and

throat (Refs. 6 and 7). They aid in the relief of sore throat and sore mouth or both by providing a protective coagulum over irriated or ulcerated surfaces. The relief is merely symptomatic and not due to any curative effects.

The protein-precipitating properties of soluble zinc salts confer varying degrees of antimicrobial activity on these compounds, but the Panel does not recognize the use of these salts as antimicrobial agents because of the variability of their action and the fact that certain specific organisms are not affected by these agents. Zinc chloride, in concentration of 5 percent or more, has been used as an escharotic agent on granulations, ulcers, and similar lesions. The acetate and sulfate are less irritating than the chloride and are preferred when a mild astringent action is desired.

(3) *Dosage.* Adults and children 3 years of age or older: Use a 0.1- to 0.25-percent concentration of zinc chloride in the form of a rinse or mouthwash or by swabbing the affected area with a cotton applicator, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The panel recommends the Category I labeling for products containing oral health care astringent active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

**References**

(1) Windholz, M., editor, "Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 1307–1308, 1976.

(2) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gillman, Macmillan Publishing Co., New York, p. 1001, 1975.

(3) Sollmann, T., "A Manual of Pharmacology and Its Application to Therapeutics and Toxicology," 2d Ed., W. B. Saunders Co., Philadelphia, pp. 917–919, 1922.

(4) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1255, 1973.

(5) Prasad, A. S., "Clinical, Biochemical, and Pharmacological Role of Zinc," *Annual Review of Pharmacology and Toxicology,* 20:393–426, 1979.

(6) OTC Volume 130003.

(7) OTC Volume 130059.

### Category I Labeling

a. *Indication.* "Aids in the temporary relief of occasional discomfort due to minor irritations of the mouth and throat."

b. *Warnings*—(1) *For all products containing oral health care astringent active ingredients.* (i) "Severe or persisent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For oral health care products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which astringent active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC astringent oral health care drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredient**

Tincture of myrrh

*Tincture of myrrh.* The Panel concludes that tincture of myrrh is not safe and not effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel has classified tincture of myrrh as a Category II antimicrobial agent and has described its general characteristics elsewhere in this document. (See part IV. paragraph B.2.j. above—Tincture of myrrh.)

(1) *Safety.* The Panel concludes that tincture of myrrh is not safe as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel has described the safety of tincture of myrrh elsewhere in this document. (See part IV. paragraph B.2.j. (1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that tincture of myrrh is not effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel finds no controlled studies which substantiate claims that tincture of myrrh is an effective active ingredient with astringent activity (Ref. 1). Tincture of myrrh has been applied locally, allegedly to "stimulate spongy gums" and as a "protectant" for aphthous ulcers, sore mouth, and ulcerations of the throat (Refs. 2 and 3). Its effectiveness for this purpose is not substantiated with data from controlled studies. Tincture of myrrh has been employed in mouth rinses in the diluted form to treat stomatitis, but data on its effectiveness are not convincing. It has been used internally as a carminative (Ref. 3).

The Panel concludes that because tincture of myrrh is a mixture of many substances and no single ingredient has been identified in the mixture that is present in sufficient quantity to exert a therapeutic effect it has no place in modern therapeutics. Tincture of myrrh since has fallen into disuse in general medical practice and has been supplanted by other medicines whose therapeutic effectiveness as astringents has been established.

(3) *Evaluation.* The Panel concludes that tincture of myrrh is an oleoresin containing various substances which are irritating to the mucous membranes of the mouth and throat. Therefore it is not considered safe for topical application on these areas. The Panel also concludes that tincture of myrrh is a mixture of many substances, none of which appear to possess any astringent action.

**References**

(1) OTC Volume 130003.

(2) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 875–877, 1955.

(3) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 170, 1957.

### Category II Labeling

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use, or for description of product attributes for products containing astringent active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Temorpary relief of minor mouth and throat pain of aphthous ulcers."

(2) "Helps kill mouth germs."

(3) "Works directly on throat membranes."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Acts fast."

(2) "Quick relief of discomfort."

(3) "Has long-lasting beneficial effect."

(4) "Exerts a prolonged action."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Formula in use over ninety years."

(2) Adding such phrases as "plus," etc.

(3) "Superior new formulation."

(4) "A dentist's formula."

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* (1) "For pain after dental work."

(2) "Relief of uncomfortable conditions of the mouth and throat."

e. *Statements or phrases in the indications for use that state or imply that a product is to be used to treat a disease process or lesion, the diagnosis of which must be made by a physician.* (1) "Relief of pain from aphthous ulcers (canker sores)."

(2) "Relieves stomatitis."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom or disease state when proof that this occurs is lacking.* (1) "Helps prevent infection in burns, abrasions and minor cuts."

(2) "As an adjunct to oral prophylaxis."

(3) "Prophylaxis for Vincent's infection."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "As an adjunct to oral hygiene."

(2) "Helps remove mouth odors."

(3) "Helps the mouth feel clean."

(4) "For hygienic care of the mouth and throat."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic or therapeutic action or class of a drug or the type of formulation containing the ingredients instead of designating the symptoms which the product is intended to relieve.* (1) "Astringent."

(2) "Mouthwash."

(3) "Gargle."

(4) "Provides protective coating to mouth sores."

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* None.

## VI. Debriding Agents

### *A. General Discussion*

1. *General comments.* Debriding agents are ingredients that soften, loosen, and remove exudates, mucus, and other secretions from the surface of irritated mucous membranes and lesions in the mouth and throat. Among these are peroxides, aqueous solutions of salts and detergents, hygroscopic agents, and enzymatic products. Debriding agents are exogenously applied to the mucous membranes to cleanse their surfaces. They differ from expectorants, which act endogenously by increasing the output of respiratory tract fluid.

a. *Mode of action.* Debriding agents act in a variety of ways. They may act mechanically, chemically, biochemically, physiochemically, or by any combination of these mechanisms. The peroxides are useful as debribing agents because they aid in the removal of debris from the mucosal surfaces by mechanical action. This results from the release of bubbles of oxygen by enzymatic activity when peroxides come into contact with the tissues. Solutions of electrolytes, such as sodium bicarbonate and saline, likewise act as debriding agents by mechanically washing the secretions from a surface. Mucus and certain secretions are softened or made fluid by alteration in pH. There is some evidence that increasing the alkalinity plays a role in reducing the tenacity and viscosity of mucus. Sodium bicarbonate is believed to act in this manner. Agents that soften or make the mucus less viscous are usually referred to as mucolytic agents. Detergents act as debriding agents by lowering surface tension. Certain enzymes may depolymerize mucopolysaccharides and render them less viscous.

Hypertonic sodium chloride solutions have been recommended for use as debriding agents since they act by osmosis and draw fluid out of tissues and cleanse mechanically. Hygroscopic agents, such as propylene glycol and glycerine, may also be applied topically to extract water from the tissues of the mouth and throat and thus reduce the viscosity of secretions and also act mechanically as cleansing agents.

Acetylcysteine allegedly reduces the viscosity of mucus in vitro by depolymerizing mucopolysaccharides. Detergents decrease surface tension and increase the wetting of tissues, thereby acting as cleansing agents. Supposedly they increase liquefaction of mucus.

b. *Use of debriding agents.* Debriding agents are used to aid in the symptomatic relief of sore mouth and sore throat. Thick, tenacious mucus, purulent secretions, and debris from desquamated cells may stimulate pain receptors in lesions such as ulcerations or inflamed areas of the mouth and throat. The removal of such secretions eliminates the stimulation and this relieves any ensuing discomfort. Debriding agents are not curative in any sense. They possess no direct, local anesthetic activity. They aid in relieving pain primarily by their protectant action. The effects of debriding agents are usually transient and of short duration, but the resultant relief of symptoms may outlast their duration of action. The peroxides, for example, may exert their debriding effects in a matter of minutes, but the relief of symptoms may last several hours.

c. *Absorption of debriding agents.* Most of the debriding agents described above are absorbed from the mucous membranes or from the gastrointestinal tract if swallowed. All those mentioned above are safe, since they are nontoxic unless used in excess or too frequently.

d. *Adverse reactions.* Adverse reactions may occur from the use of debriding agents, particularly from overuse. Overuse of the peroxides has caused sloughing of the mucous membranes. Inflammatory reactions may also occur from long-term use since some debriding agents may be locally irritating. Gastrointestinal disturbances may occur when some debriding agents are swallowed. The desiccating agents may cause dryness and enhance the severity of inflammatory lesions. Solutions that are excessively hypertonic may also act as desiccating agents and aggravate the symptoms. Sensitization may occur, but has not been reported following use of the debriding agents evaluated by the Panel.

### *B. Categorization of Data*

1. *Category I conditions under which debriding agents for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

**Category I Active Ingredients**

Carbamide peroxide in anhydrous glycerin (urea peroxide)
Hydrogen peroxide
Sodium bicarbonate

a. *Carbamide peroxide in anhydrous glycerin (urea peroxide).* The Panel concludes that carbamide peroxide in anhydrous glycerin is safe and effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The general properties and safety of carbamide peroxide have been described above as an antimicrobial ingredient for use on the mucous membranes of the mouth and throat.

(See part IV. paragraph B.3.d. above—Carbamide peroxide in anhydrous glycerin (urea peroxide).)

(1) *Safety.* The Panel concludes that carbamide peroxide in anhydrous glycerin is safe as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

It is the consensus of the Panel that the comments concerning the safety of carbamide peroxide as an antimicrobial agent are likewise applicable to its use as a debriding agent on the mucous membranes of the mouth and throat. (See part IV. paragraph B.3.d.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that carbamide peroxide is an effective OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Carbamide peroxide is dissolved in anhydrous glycerin or propylene glycol (Ref. 1). It is slowly decomposed into its components, urea and hydrogen peroxide, when it comes into contact with moisture, air, or light. When applied to living tissue, ulcerations of the mucous membrane, or mixed with saliva, blood, or other body tissue fluid or exudates containing the enzyme catalase, oxygen is released from the hydrogen peroxide in the form of fine bubbles. This causes frothing and foaming which aids in the dislodgement of dead, desquamated eipthelial cells, pus, or other organic material found in infected wounds and on ulcerations which effect their removal (Refs. 2 and 3). One part of carbamide peroxide releases five volumes of oxygen. The byproducts of the breakdown of carbamide peroxide are oxygen, water, and urea (Ref. 4). Tissues that contain peroxidases also cause the breakdown of hydrogen peroxide to oxygen, urea, and water, but the oxygen combines with a hydrogen acceptor and no free oxygen is released. Under these circumstances the ingredient would not be effective. The urea exerts no known therapeutic effect since urea is a normal constituent of body tissues resulting from the metabolism of protein. It exerts no known adverse effects on the mucous membranes since the quantity released in this reaction is not significant. In aqueous solutions the compound slowly decomposes, releasing oxygen, urea, and byproducts of its decomposition. This renders the preparation ineffective.

(3) *Dosage.* Adults and children 3 years of age or older: Use a 10.0- to 15.0-percent concentration of carbamide peroxide in anhydrous glycerin undiluted by swabbing the affected area or use a 10.0- to 15.0-percent aqueous solution of carbamide peroxide in the form of a rinse, gargle, or spray, not more than three to four times daily. For children under 3 years of age, there is no dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care debriding agent active ingredients. (See part VI. paragraph B.1. below—Category I Labeling.)

**References**

(1) Dale, J. K., and R. E. Booth, "Physical and Chemical Incompatibilities," *in* "Dispensing of Medication," 7th Ed., edited by E. W. Martin, Mack Publishing Co., Easton, PA, p. 284, 1971.

(2) OTC Volume 130016.

(3) OTC Volume 130017.

(4) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1266, 1976.

b. *Hydrogen peroxide.* The Panel concludes that hydrogen peroxide is safe and effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The general characteristics of hydrogen peroxide have been described elsewhere in this document. (See part IV. paragraph B.3.m. above—Hydrogen peroxide.)

(1) *Safety.* The Panel concludes that hydrogen peroxide is safe as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Hydrogen peroxide is safe, when used as a 3-percent aqueous solution or when diluted with equal parts of water, for topical use on the mucous membranes of the mouth and throat.

The safety of hydrogen peroxide has been described elsewhere in this document. (See part IV. paragraph B.3.m.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that hydrogen peroxide is effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The effectiveness of hydrogen peroxide as an antimicrobial agent for use on the mucous membranes of the mouth and throat has been described elsewhere in this document. (See part IV. paragraph B.3.m.(2) above—Effectiveness.)

The usefulness of hydrogen peroxide as a debriding agent depends upon the release of nascent oxygen which presumably has a strong oxidizing effect and may chemically alter organic substances found in wounds and ulcerations of the mucous membranes and in pus.

When hydrogen peroxide comes into contact with tissues, it is converted to water and oxygen due to the action of the enzyme catalase. This reaction occurs very rapidly, and the bubbles of oxygen that are released effervesce, thereby loosening tissue, debris, mucus, pus, and other organic materials (Refs. 1, 2, and 3).

The release of oxygen occurs more rapidly in open wounds, on ulcerations, and on denuded areas of mucous membranes than it does on intact mucous membranes. It occurs in a healthy mouth since catalase is normally present in the saliva. Particles of food and debris present in the mouth and between the teeth may be dislodged. Little or no oxygen is released when hydrogen peroxide is applied to intact skin. The duration of action of hydrogen peroxide is brief because decomposition occurs very rapidly.

Removing organic debris by the mechanical action of oxygen release is probably the most important attribute of hydrogen peroxide. It is believed to be more so than its antimicrobial activity, since there is some doubt as to its effectiveness as an antimicrobial agent. This debriding action may aid in the relief of pain and discomfort due to sore throat and sore mouth. (See part IV. paragraph B.3.m.(2) above—Effectiveness.)

Hydrogen peroxide may be used full strength, but generally it is diluted with an equal volume of water. When used in closed cavities such as nasal sinuses for cleansing and irrigation, it is important that there be a vent for the escape of gas, otherwise pressure may be generated within a cavity of such magnitude to cause serious local injury. Furthermore, the unvented gas may even cause air emboli. The possibility that this may occur when hydrogen peroxide is used in the mouth or in the throat is remote, since all the spaces are free and open.

Prolonged topical use causes irritation of the buccal mucous membranes and, therefore, it should not be used more often than every 2 hours, for not more than 2 days.

(3) *Dosage.* Adults and children 3 years of age or older: Use a 3.0-percent concentration of hydrogen peroxide diluted with equal parts of water in the form of a rinse, mouthwash, gargle or spray, or apply with a swab, not more

than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care debriding agent active ingredients. (See part IV. paragraph B.1. below—Catetory I Labeling.)

**References**

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 36th Ed., American Dental Association, Chicago, p. 207, 1975.

(2) Darlington, R. C., "Topical Oral Antiseptics, Mouthwashes and Throat Remedies," *in* "Handbook of Non-Prescription Drugs," 4th Ed., edited by G. B. Griffenhagen and L. L. Hawkins, American Pharmaceutical Association, Washington, p. 131, 1973.

(3) Stecher, P. G., editor, "The Merck Index," 8th Ed., Merck and Co., Rahway, NJ, p. 545, 1968.

c. *Sodium bicarbonate.* The Panel concludes that sodium bicarbonate is safe and effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Sodium bicarbonate is also known as sodium hydrogen carbonate or sodium acid carbonate. Among consumers, it is known as baking soda. Its empirical formula is $NaHCO_3$ and it has a molecular weight of 84. The commercial preparation available in pharmacies and in groceries is 99.8 percent pure (Ref. 1).

Sodium bicaronate is a white crystalline powder or a powder consisting of granules. It begins to lose carbon dioxide at about 50° C (Ref. 1). At 100° C it is converted to sodium carbonate ($NA_2CO_3$), which is more alkaline. In a vacuum, sodium bicarbonate will release carbon dioxide. Sodium bicarbonate is readily decomposed into the salt of the acid and carbon dioxide by weak acids. In aqueous solutions, it begins to change into carbon dioxide and sodium carbonate at about 20° C and changes completely upon boiling. Sodium bicarbonate is soluble in 10 parts of water at 25° C and 12 parts of water at about 18° C. It is insoluble in alcohol (Ref. 1). Aqueous solutions of sodium bicarbonate prepared with cold water, without agitation, are slightly alkaline. Aqueous solutions slowly decompose on standing to carbon dioxide and sodium carbonate. The alkalinity increases due to this gradual conversion to sodium carbonate. The pH of solutions of sodium carbonate generally is between 8.0 and 8.2.

(1) *Safety.* The Panel concludes that sodium bicarbonate is safe as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The fact that sodium bicarbonate has been used for such a long time in the preparation of various food products, in cooking, and medically in gastrointestinal disturbances attests to its safety. It has been used as an antacid for gastric hyperacidity, peptic ulcer, to alkalinize the urine in cases of urinary hyperacidity, and intravenously to correct the acid base balance in cases of acidosis, shock, etc. (Ref. 2).

When sodium bicarbonate is ingested, it interacts with the hydrochloric acid of the stomach. It is then converted to sodium chloride and carbon dioxide with the carbon dioxide often being released by belching. Externally, it has no irritating effect, and it has not been found to have any sensitizing effect on the mucous membranes (Ref. 3). The chief danger in the use of sodium bicarbonate lies in its overuse. This is particularly significant in the case of individuals with heart disease, hypertension, and renal disease, who must restrict their sodium ion intake. Sodium bicarbonate is not caustic to the skin or mucous membranes of the oral cavity. It is sometimes used as a paste for cleansing teeth and on the skin to relieve itching.

(2) *Effectiveness.* The Panel concludes that sodium bicarbonate is effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Sodium bicarbonate has been used parenterally to correct acidosis. It is also used externally as a cleansing agent in infections, for burns, scalds, urticaria, and various skin diseases. Sodium bicarbonate has been used as a cleansing douche in cases of vaginitis. The powder is orderless with a slightly saline and alkaline taste. The solution has a bitterish saline taste (Ref. 4).

Sodium bicarbonate soothes irritated skin and relieves the pain of minor acid burns. When used in a bath or as a dusting powder, it reduces the odor of sweat. Prompt application of moist sodium bicarbonate as a paste has helped relieve itching from nonpoisonous insect stings and bites (Ref. 4). Sodium bicarbonate, like other mild alkalies, combines with tissue proteins to form alkaline albuminates or with the cutaneous fats to form soaps. In this way it acts as an emollient and softens the epithelium of the skin.

Sodium bicarbonate has a mucolytic action due to its alkalinity. It favors the disintegration of mucus, separating the protein from the polysaccharide components of the mucoprotein chain. It has been used in inhalation therapy as an aerosol to liquidy the secretions of the tracheobronchial tree. When used as a spray, gargle, or rinse in the mouth and throat, it loosens and softens tenacious mucus so that expectoration is facilitated. This debriding action aids in the relief of pain and discomfort due to sore throat or sore mouth. Sodium bicarbonate possesses no antimicrobial activity, nor does it possess any analgesic properties. It is sometimes classed with expectorants, but it has no well defined expectorant activity. The debriding and mucolytic actions of aqueous solutions of sodium bicarbonate are primarily mechanical and chemical.

Sodium bicarbonate increases the alkalinity of the saliva of the mouth and throat, but this is temporary. Fresh saliva is constantly being secreted, and the sodium bicarbonate is washed away, restoring the original pH of the mouth.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 5.0- to 10.0-percent concentration of sodium bicarbonate combined with one-half teaspoonful of sodium chloride in a glass of warm water in the form of a gargle, not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care debriding agent active ingredients. (See part VI. paragraph B.1. below—Category I Labeling.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1109, 1976.

(2) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, pp. 1033–1034, 1977.

(3) OTC Volume 130025.

(4) Harvey, S.C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 966, 1975.

(5) Swinyard, E. A., "Gastrointestinal Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., p. 736, 1975.

**Category I Labeling**

a. *Indication.* "Aids in the removal of phlegm, mucuc, or other secretions in

the temporary relief of discomfort due to occasional sore throat and sore mouth."

b. *Warnings*—(1) *For all oral health care products containing debriding agent active ingredients.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use for more than 2 days or administer to children under 3 years of age unless directed by physician."

(ii) "Discontinue use and consult a physician if irriation persists or increases, or if a rash appears on the skin."

(2) *For oral health care products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which debriding active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral health care drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredients**

Sodium perborate.

*Sodium perborate.* The Panel concludes that sodium perborate is not safe and not effective for use as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel has classified boric acid and other derivatives containing elemental boron as Category II ingredients for use in the mouth and throat. The general characteristics of boron derivatives have been described elsewhere in this document. (See part IV. paragraph B.2.a. above—Boric acid.)

Sodium perborate is a white, crystalline powder, which is odorless, has a saline taste, and is stable in cool, dry air. It is decomposed with the evolution of oxygen in warm, moist air. In aqueous solutions sodium perborate decomposes into sodium metaborate and hydrogen peroxide. The solution gradually evolves oxygen. Heating accelerates the release of oxygen. One gram of sodium perborate dissolves in 40 mL of water (Ref. 1).

Sodium perborate is prepared by the interaction of boric acid or sodium borate with sodium or hydrogen peroxide. It is generally considered to be a derivative of pentavalent boron. Actually, sodium perborate is derived from the tribalent form and has a composition believed to be $NaBO_2 \cdot H_2 \cdot 3H_2O$. It contains less than 9 percent available oxygen by weight. Sodium perborate is decomposed by water to hydrogen peroxide and sodium metaborate (Ref. 2). Its decomposition is accelerated by enzymes found in the tissues in the mouth and in saliva such as catalase.

Sodium perborate is not considered safe because it is a derivative of boron, and when absorbed it is as toxic as boric acid and other boron derivatives. The Panel found no data concerning the acute or chronic toxicity of sodium perborate in animals or in man (Refs. 3, 4, and 5). Inasmuch as sodium perborate is unstable and decomposes on standing, to sodium metaborate and sodium borate, the Panel considers the data on the toxicity of boric acid to be applicable to sodium perborate. Continued use of sodium perborate causes hypertrophy of the papillae of the tongue and damage to the gums.

(1) *Safety.* The Panel concludes that sodium perborate is not safe as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel has described the safety of boric acid and boron toxicity elsewhere in this document. (See part IV. paragraph B.2.a.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that sodium perborate is not effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat.

Sodium perborate has been used extensively in past years as an antiseptic for wounds (Ref. 6). Its antimicrobial activity is ascribed to its oxidizing effects resulting from the release of nascent oxygen (Ref. 7). A 2-percent solution was found to be as effective as an approximately 0.4-percent solution of hydrogen peroxide. It has also been used as a dusting powder combined with talc and other inert ingredients. Sodium perborate has been most frequently used for preparations of antiseptic mouthwashes for the treatment of acute necrotic ulcerogingivitis (Vincent's infection) (Ref. 7). The alkalinity of solutions of sodium perborate assists in the removal of mucus and food residues in the mouth and throat (Ref. 7). The instability of the solution requires that it be prepared at the time of usage. A saturated solution represents 2 percent of the salt. Ten to 20 percent is mixed with chalk for use as a dentifrice.

The alleged effectiveness of sodium perborate as a debriding active ingredient is believed to be due to the alkalinity of the solution and oxygen that is released when sodium perborate comes in contact with tissues, open wounds, and ulcerations.

(3) *Evaluation.* It is the consensus of the Panel that the quantity of oxygen released when sodium perborate is applied to tissues is insufficient to act mechanically as a debriding agent. Furthermore, sodium perborate is prepared from boric acid and is therefore a derivative containing elemental boron. It is not safe for use on the mucous membranes of the mouth and throat since it can undergo systemic absorption and be toxic. Sodium perborate is therefore placed in Category II from the standpoint of both safety and effectiveness.

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1118, 1976.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 843, 1957.

(3) OTC Volume 130048.

(4) OTC Volume 130071.

(5) OTC Volume 130093.

(6) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, p. 892, 1977.

(7) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1072–1073, 1973.

**Category II Labeling**

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use or for description of product attributes for products containing debriding agent active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Healing aid for minor oral inflammation."

(2) "Cleansing antiseptic for mouth and throat."

(3) "Antimicrobial cleansing agent."

(4) "Provides temporary pain relief."

(5) "Promotes flow of saliva."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Quickly removes phlegm and other secretions."

(2) "Fast acting."

(3) "Has long-lasting beneficial effects."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Superior cleansing agent."

(2) "Rapid acting with long lasting effects."

(3) Adding such phrases as "plus," etc.

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* (1) "Forming, cleansing rinse for irritated throats."

(2) "Removes secretions causing sore throat caused by postnasal drip."

e. *Statements and phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion, diagnosis of which must be made by a physician.* (1) "Helps against discomfort of canker sores."

(2) "Helps reduce inflammation."

(3) "For treatment of stomatitis."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom or disease state when proof that this occurs is lacking.* (1) "Removes disease causing germs by its cleansing action."

(2) "Prevents growth of odor forming bacteria."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "For mouth and gum care."

(2) "Soothing and cleansing to the mouth and throat."

(3) "A refreshing mouth rinse."

(4) "For oral hygiene."

(5) "Destroys odor forming germs."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic effect or class of a drug or the formulation containing the ingredient instead of designating the symptoms which the product is intended to relieve.* (1) "Debriding agent."

(2) "Mouthwash."

(3) "Gargle."

(4) "Cleansing agent."

(5) "Mouth rinse."

(6) "Cleansing antiseptic for the mouth and throat."

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* None.

## VII. Decongestants

### *A. General Discussion*

1. *General comments.* The vasomotor integrity of the mucosa of the naso- and oro-pharnyx and mouth depends upon the proper balance between sympathetic and parasympathetic efferent impulses. Activation of the parasympathetic division of the autonomic nervous system produces vasodilatation and increases secretions from the exocrine glands. Activation of the sympathetic division produces vasoconstriction and decreases glandular secretion.

Congestion of the mucosa of the upper respiratory tract is manifested by the engorgement of the blood vessels in the mucosa and passage of fluid from the capillaries into the tissue spaces. Congestion is usually caused by microbial infection, chemical irritation, allergy, and other such factors. Treatment is usually directed toward removing the cause. The symptoms may be relieved by eliciting sympathetic responses or blocking parasympathetic responses. Drugs that produce these responses and causes constriction of the blood vessels are called decongestants.

a. *Mode of action.* Stimulation of the parasympathetic nervous dilates the blood vessels and also activates the saliva and mucous glands causing an increase in secretions of saliva and mucus from the glands of the mucous membranes. Stimulation of the parasympathetic nervous system may aggravate the congestion. Activation of the sympathetic division usually does the reverse and relieves congestion. It may cause a thick mucous secretion to be released. Some alpha adrenergic drugs also possess a mild beta-stimulating vasodilating action. This is overshadowed by the alpha effect, but lingers on when the shorter alpha action has receded. Vasodilation may occur from this beta stimulation, causing a rebound effect and a return of symptoms of congestion.

Adrenergic agents are most commonly used for the symptomatic relief of nasal congestion. Adrenergic agents act by stimulating the alpha excitatory adrenergic receptors of the vascular smooth muscle, thus constricting the network of arterioles within the mucosa and reducing the flow of blood in the engorged edematous area. Opening of the obstructed nasal passages improves nasal ventilation and facilitates the aeration and drainage of the sinuses. Most decongestants are used topically, or ingested orally, or used in both ways. The response to topical application of nasal decongestants is prompt but variable in duration, whereas the response to oral therapy is slow and generally less intense and of longer duration. The nasal mucous membrane is more turgid than the oral and pharyngeal mucous membranes, and shrinkage is more obvious when decongestant drugs are applied to the nasal mucosa. The other mucous membranes, such as those of the mouth and throat, also respond to the action of vasoconstrictors.

b. *Uses of decongestants.* The Panel has considered the decongestant active ingredients and has deferred most of them to the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products for evaluation since they are administered orally or parenterally and act systemically. Ordinarily labeling claims for topical use are made for their nasal effects. However, in evaluating certain products in the submissions, the Panel found that some decongestants were combined with other topically active ingredients in the form of lozenges. The labeling implied that the decongestant also acted locally on the mucous membranes of the throat and mouth. The Panel therefore felt obligated to evaluate the topical effects of these decongestants on the mucous membranes of the mouth and throat. The Panel noted that the quantities of decongestant ingredients incorporated in the product were less than the minimum recommended for a single dose for oral use by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. The Panel also noted that effectiveness of decongestants that are used topically in a "slow-release" dosage form, as would be the case when incorporated in a lozenge, was not considered by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. In view of the fact that the topical application of these products stimulates adrenergic vasoconstriction locally, the Panel felt that these products should be evaluated from the standpoint of the local effect on the mucous membranes of the mouth and throat. No data were found to support the claim that decongestants are effective topically on the mucous membranes of the mouth and throat, or that the resulting vasoconstriction, should it occur, was of therapeutic benefit. On the other hand, there were no data available contradicting the fact that this occurs. The Panel, therefore, feels that in view of this lack of data, the decongestants mentioned in the products whose labeling indicates or implies that topical activity occurs in the mouth and throat, particularly the latter, should be considered with the oral health care products. In addition the Panel notes that vasoconstrictors combined with local anesthetics may prolong the analgesic effect by retarding the absorption of the drug.

c. *Adverse effects.* The topical application of decongestants sometimes

causes temporary discomfort, such as stinging, burning, or dryness of the mucosa. Various other adverse effects can be cited. One of the major disadvantages of the use of adrenergic blocking agents is the occurrence of rebound congestion after the vasoconstrictive action disappears. This is due to the fact that the beta stimulating effect of the drug lingers after alpha stimulation disappears. Some decongestants stimulate both beta and alpha receptors, and beta stimulation causes vasodilation. Recurrence or exacerbation of the original discomfort may cause the patient to apply or inhale the drug more frequently. Overdosage with signs of toxicity may result. Irritation from prolonged and continued use produces chronic swelling of the nasal mucosa. Whether or not this occurs in the oral mucosa has not been determined.

Topical decongestants also produce systemic reactions especially in infants and children or patients with cardiovascular diseases, hyperthyroidism, or patients taking monoamine oxidase inhibitors. Significant absorption can occur from the mucosa of the nasopharynx and the oropharynx, or from the gastrointestinal tract, when an excess of the solution trickles down the throat and is swallowed. Topical application of the decongestant may be the best way to avoid systemic absorption. Use of a spray held in the upright position minimizes accumulation since the medication and secretions drip from the nostril and are swallowed.

The systemic effects from overdosage of most adrenergic drugs include transient hypertension, tachycardia, nervousness, nausea, dizziness, palpitation, and occasionally central nervous system stimulation.

Adrenergic agents should be given sparingly and with caution to patients with hyperthyroidism, hypertension, diabetes mellitus, or ischemic heart disease.

*B. Categorization of Data*

1. *Category I conditions under which decongestant active ingredients for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

**Category I Active Ingredients**

None.

**Category I Labeling**

a. *Indication.* The Panel did not classify any decongestant active ingredient in Category I, but did place some ingredients in Category III. Because additional testing is necessary to determine the actual effect these ingredients have in the mouth and throat, the Panel has proposed a Category III indication for decongestant active ingredients. (See part VII. paragraph B.3. below—Category III Labeling.)

b. *Warnings*—(1) *For all decongestant drug products.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

(3) *For products containing phenylephrine hydrochloride or phenylpropanolamine hydrochloride.*

(i) "Do not use if taking monoamine oxidase inhibitors. Discontinue use if dizziness, headache, fast pulse, tremors, or nervousness develop. Consult a physician if symptoms persist."

(ii) "Do not use this product if you have thyroid disease, high blood pressure, diabetes, or heart disease except under the advice and supervision of a physician."

2. *Category II conditions under which decongestant active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The panel recommends that the Category II conditions be eliminated from OTC decongestant oral health care drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredients**

None.

**Category II Labeling**

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use or for description of product attributes for products containing decongestant active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statement or phrases which purport that a product exerts a pharmocologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Quiets rasping cough due to colds which may be causing discomfort."

(2) "For temporary relief of minor sore throat pain."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of ways by consumers, rather than in definite units of time.* (1) "Fast temporary relief of minor throat irritations."

(2) "Provides long lasting relief of mouth and throat discomfort."

(3) "Promotes healing."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Superior decongestant."

(2) "Multiaction formulation."

(3) Adding such terms as "plus," etc.

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* (1) "Soothes tired throats."

(2) "Makes breathing easier."

(3) "Fights sore throat."

e. *Statements or phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion, the diagnosis of which must be made by a physician.* (1) "Relieves sore throat pain due to postnasal drip."

(2) "Reduces inflammation."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom of disease state when proof that this occurs is lacking.* (1) "Helps prevent infection."

(2) "As an adjunct to prevent Vincent's infection."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "Reduces mouth odors."

(2) "Makes mouth feel clean."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic or therapeutic action or class of a drug or type of formulation containing the ingredients instead of designating the symptoms which the product is intended to relieve.* (1) "Decongestant for use on mucous membranes."

(2) "Oral spray."

(3) "Lozenge."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

**Category III Active Ingredients**

Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride

a. *Phenylephrine hydrochloride.* The Panel concludes that phenylephrine hydrochloride is safe, but that there are insufficient data available to permit final classification of the effectiveness of phenylephrine hydrochloride as an OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenylephrine is the levo isomer of 3-hydroxyphenylethanol methylamine. In essence, it is epinephrine minus one hydroxyl group on the benzene ring at position number four (Ref. 1). The existing hydroxyl group is on position three. Phenylephrine is a synthetic, optically active sympathomimetic amine. It is a white, odorless, powder consisting of bitter-sweet crystals which are freely soluble in water or alcohol. Aqueous solutions of phenylephrine hydrochloride are either slightly acidic, or they are neutral to litmus. Phenylephrine hydrochloride melts between 140° to 145° C (Ref. 2). Phenylephrine acts at the alpha receptors. It is less potent than epinephrine, but is longer lasting.

(1) *Safety.* The Panel concludes that phenylephrine hydrochloride is safe as an OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenylephrine hydrochloride is safe and has a low degree of toxicity in man. The subcutaneous $LD_{50}$ in mice is 1 g/kg. According to Gleason and associates (Ref. 3), the toxicity rating is 5. Phenylephrine hydrochloride is absorbed from the oral and gastric mucous membranes and produces a systemic sympathomimetic effect. Mild gastrointestinal symptoms are sometimes observed when large doses are administered by the oral route.

When the drug is administered intravenously, it produces an intense vasoconstriction and an elevation in diastolic and systolic pressure and a bradycardia (Ref. 4). The bradycardia is due to reflex vagal stimulation. Phenylephrine hydrochloride lacks a positive inotropic effect on the heart, which would increase the strength of that organ's muscular contraction. In large intravenous doses, it may produce intense vasoconstriction, a reflex bradycardia, and various types of arrhythmias. In cases of heart failure, it may cause pulmonary edema. With lesser intravenous dosages, ventricular extrasystoles and short paroxysms of ventricular tachycardia may occur. A sensation of fullness of the head and tingling of the extremities, likewise, is noted. Tremor, palpitation, and insomnia may occur in some patients. The pressor effect produced by sympathomimetic amines is markedly potentiated by monoamine oxidase inhibitors. Excessive elevation in blood pressure and hypertensive crises may occur when such drugs are used simultaneously (Ref. 1).

Parenteral or oral administration or topical use of phenylephrine hydrochloride may be contraindicated in patients with cardiovascular diseases, hypertension, severe arteriosclerosis or in patients with hyperthyroidism accompanied by tachycardia (Ref. 1). Phenylephrine hydrochloride solutions are contraindicated either topically or orally in persons with narrow-angled glaucoma. Overdosage of phenylephrine hydrochloride in susceptible individuals has resulted in a marked evaluation in blood pressure followed by cerebrovascular accidents. A reflex bradycardia results from the absorption of phenylephrine hydrochloride. This may be counteracted by atropine since it is due to reflex vagal stimulating effect. Phenylephrine hydrochloride should not be used simultaneously with monoamine oxidase inhibitors.

Solutions for topical use are sometimes preserved with agents such as sodium bisulfite, chlorobutanol, or methylparaben. These agents may cause local irritation or sensitization.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of phenylephrine hydrochloride as an OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenylephrine hydrochloride is an effective alpha adrenergic drug that causes vasoconstriction and produces decongestion of mucous membranes when applied topically. Subsequently, parenteral phenylephrine hydrochloride produces an increase in arterial blood pressure and a reflex bradycardia without appreciably increasing the heart rate or cardiac output. Phenylephrine hydrochloride has little or no central stimulating action as does ephedrine and the amphetamine-type sympathomimetic drugs. Responses to phenylephrine hydrochloride are both locally and systemically more prolonged than with epinephrine.

Phenylephrine hydrochloride is used topically in a 0.25- to 1.0-percent solution as a nasal decongestant (Ref. 5). In some cases, it may produce marked local irritation. Phenylephrine hydrochloride acts by stimulating the alpha adrenergic receptors of the vascular smooth muscle of the mucous membranes of the nose, throat, and mouth, thus constricting the dialated network of arterioles and reducing the flow of blood (Refs. 6 and 7). This is most apparent in the nose since the mucous membranes are turgid in this area. Excessive use may produce congestion of the mucosa, and if sufficient quantities are absorbed, an elevation in blood pressure, dizziness, palpitations, and central nervous stimulation are sometimes observed. The secondary congestion of the mucous membranes is due to at least three factors, i.e., secondary vasodilation due to stimulation of beta adrenergic fibers by the phenylephrine hydrochloride effect which lingers beyond its alpha stimulatory action, increased capillary permeability due to vasoconstrictive ischemia, and local irritation. Phenylephrine hydrochloride has a low degree of irritancy and sensitizing potential.

Phenylephrine hydrochloride has been used in lozenges, with local anesthetics and other active ingredients to relieve sore throat (Ref. 8). There are no well-controlled studies demonstrating the effectiveness of phenylephrine hydrochloride as an effective decongestant on the mucous membranes of the mouth or throat nor is there sufficient evidence from controlled studies to indicate that decongestants provide symptomatic relief for irritation and pain or soreness of the mucous membranes of the mouth or throat. Phenylephrine retards the absorption of topically applied local anesthetics from the mucous membranes and prolongs their action.

The Panel notes that phenylephrine hydrochloride has been deferred to the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products for evaluation of its effectiveness systemically, when taken orally. The dosage recommended by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products as a Category I ingredient is 10 mg. The dose in the lozenge of the product submitted to the Oral Cavity Panel for evaluation is 5 mg (Ref. 8). The labeling for the

lozenge does not state if the ingredient acts systemically or topically. The implication is that it acts topically. The Oral Cavity Panel recommends that the mode of action be clarified in the labeling. If a topical action is meant, the labeling should so indicate. If the action is systemic the dose should conform to the recommended oral dose of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products, and the labeling should state that topical administration of this dose is effective systemically. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products has not so stated.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use 5.0 mL of a 0.25-percent concentration of phenylephrine hydrochloride in normal saline in the form of a swab or spray, not more than three to four times daily. Use a lozenge containing 5 mg of phenylephrine hydrochloride every 2 hours if necessary. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care decongestant active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care decongestant active ingredients. (See part VII. paragraph B.3. below—Category III Labeling.)

In addition, the Panel also recommends the following specific labeling:

*Warnings.* (i) "Do not use if taking monoamine oxidase inhibitors. Discontinue use if dizziness, headache, fast pulse, tremors, or nervousness develop. Consult a physician if symptoms persist."

(ii) "Do not use this product if you have thyroid disease, high blood pressure, diabetes, or heart disease except under the advice and supervision of a physician."

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care decongestants. (See part VII. paragraph C. below—Data Required for Evaluation.)

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(8) OTC Volume 130058.

b. *Phenylpropanolamine hydrochloride.* The Panel concludes that phenylpropanolamine hydrochloride is safe, but that there are insufficient data available to permit final classification of the effectiveness of phenylpropanolamine hydrochloride as an effective OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenylpropanolamine hydrocholoride is related structurally to the amphetamines (Refs. 1 and 2). It differs from ephedrine is having one less methyl radical and differs from the amphetamines in having a hydroxyl group on the aliphatic side chain. Thus, phenylpropanolamine hydrochloride is a sympathomimetic amine related both structurally and pharmacilogically to ephedrine and the amphetamines. It exerts most of its action on alpha adrenergic receptors.

Phenylpropanolamine hydrochloride is a white, crystalline powder with a slightly aromatic odor. It is decomposed by light. It is freely soluble in water and in alcohol, but insoluble in ether. Phenylpropanolamine hydrochloride melts between 190° and 194° C. Solutions of phenylpropanolamine hydrochloride are slightly acidic. Other names for phenylpropanolamine are norephedrine hydrochloride and propadrine hydrochloride (Refs. 1 and 3).

When applied locally phenylpropanolamine hydrochloride constricts capillaries and arterioles and shrinks the swollen mucous membranes of the mouth, the oropharynx, and particularly the nasal cavity. Systemically, it exerts a pressor effect and raises the blood pressure. Phenylpropanolamine hydrochloride has a longer duration of action and produces less central stimulation than ephedrine or the amphetamines (Ref. 1).

(1) *Safety.* The Panel concludes that phenylpropanolamine hydrochloride is safe as an OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The toxicity rating by Gosselin and associates (Ref. 4) is 5. The lethal dose in man is approximately 50 mg/kg. The minimal lethal intraperitoneal dose in rats is 175 mg/kg. In mice acute toxicity is influenced by temperature. The $LD_{50}$ is lower at 32° C than at 26° C (Ref. 5). The subcutaneous $LD_{50}$ in mice is 850 mg/kg (Ref. 5). The minimal lethal dose in guinea pigs when administered subcutaneously is 600 mg/kg (Refs. 6 and 7). The intravenous $LD_{50}$ in rabbits is 75 mg/kg, and the subcutaneous $LD_{50}$ for the sulfate is 400 to 500 mg/kg (Ref. 6). In paired feeding experiments using oral doses of 2.4 mg/kg in rats for as long as 59 days, there was an initial decrease in food intake, but later, a return of the appetite. The rate of food passage through the gastrointestinal tract was decreased, but the digestion was not affected (Refs. 8 and 9).

Phenylpropanolamine hydrochloride is absorbed through the mucous membranes of the mouth and throat into the blood stream and causes a generalized sympathomimetic effect (Ref. 10). Large doses produce hypertension, headaches, tachycardia, restlessness, anxiety, sweating, tremor, extrasystoles, confusion, and delirium, whether taken orally or given parentally (Ref. 11). Administration of barbiturates partially relieves some of these symptoms. In general, untoward effects are minor in the majority of patients receiving therapeutic doses of the drug. Phenylpropanolamine hydrochloride causes a marked pressor effect if administered at the same time as monoamine oxidase inhibitors and is contraindicated for use in patients taking monoamine oxidase inhibitors (Ref. 12). It should be used with caution in patients with hypertension, cardiovascular diseases, hyperthyroidism, and diabetes (Ref. 13). It is contraindicated in patients with narrow-angle glaucoma and in patients with prostatic hypertrophy and in pregnancy.

Phenylpropanolamine hydrochloride has a low degree of irritancy and a low sensitizing potential. It interacts with

belladonna alkaloids and increases the incidence of side effects (Ref. 14). Phenylpropanolamine hydrochloride does not sensitize the heart to hydrocarbon anesthetics as do cyclopropane, chloroform, etc. (Ref. 15). Arrhythmias occur in nonanesthetized subjects due to its reflex vagal effects when the heart ejects blood against a constricted vascular bed, as is the case with other vasoconstrictors.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of phenylpropanolamine hydrochloride as a OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used in the proposed dosage limit set forth below.

There are numerous studies, both controlled and uncontrolled, on the effects of phenylpropanolamine hydrochloride as an adrenergic agent (Ref. 12). Its action is primarily stimulation of alpha adrenergic receptors, since these are located in the arterioles and venules and not in the capillaries. Its vasoconstrictor effect is largely the result of its action upon the arterioles. Phenylpropanolamine hydrochloride acts on the mucous membranes of the mouth, nose, and throat when applied topically. It is most effective as a nasal decongestant, particularly in allergic rhinitis (Ref. 16). Phenylpropanolamine hydrochloride is also employed in bronchial asthma and as an antihypotensive agent during spinal anesthesia (Refs. 17 and 18). It is of little value as an anorexiant for control of obesity (Refs. 1 and 8).

Phenylpropanolamine hydrochloride is equally as effective, if not superior, to ephedrine as a sympathomimetic amine and as a vasoconstrictor (Ref. 2). Black (Ref. 19) compared phenylpropanolamine hydrochloride with ephedrine in 131 patients and found the symptomatic relief equal to that of ephedrine, but without the annoying side effects. Boyer (Ref. 20) used 0.75 g every 2 hours for 5 days or more and found phenylpropanolamine hydrochloride significantly more effective than other preparations. Solo (Ref. 21) found a marked vasoconstrictor effect lasting for periods up to 2 hours with a 3-percent aqueous solution in 300 patient studies. When the drug was applied topically, Murphy (Ref. 16) obtained good results with 0.75 g in adults and 0.375 g in children. Phenylpropanolamine hydrochloride is also used orally to produce systemic vasoconstriction, but is much more effective when applied topically in the nose. The vasoconstriction effect is more apparent in the nose than in the mouth and throat due to the turgidity that is characteristic of nasal mucosa compared to the oral mucosa. The duration of action of phenylpropanolamine adminstered topically is 2 to 3 hours and orally is approximately 4 hours.

There are insufficient data confirming the effectiveness of phenylpropanolamine hydrochloride as a decongestant on the mucous membranes of the mouth and throat. Furthermore, there are no studies that indicate phenylpropanolamine hydrochloride does not exert a beneficial effect in treating the symptoms, lesions, inflammations, or irritations in the oral cavity, since it is a topically acting vasoconstrictor.

Phenylpropanolamine hydrochloride has been used in the form of a lozenge with claims for relief of soreness of the mucous membranes of the mouth and throat. These lozenges contain, in addition to phenylpropanolamine hydrochloride, benzocaine and phenylephrine (Ref. 22). The quantity of phenylpropanolamine is less than the minimum effective orally administered dose recommended by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products. Furthermore, that Panel has not considered the effectiveness of this ingredient systemically in subtherapeutic doses in a slow release dosage form as would be the case when incorporated in a lozenge for topical use. It is for these reasons that the Panel feels obligated to consider this ingredient in this combination. The quantity in the lozenge, if the drug acts systemically when absorbed after swallowing, is subtherapeutic.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use 5.0 mL of a 0.25-percent concentration of phenylpropanolamine hydrochloride in aqueous solution in the form of a swab or spray, not more than three to four times daily. Use a lozenge containing 10.5 mg of phenylpropanolamine hydrochloride every 2 hours if necessary. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care decongestant active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

In addition, the Panel also recommends the following specific labeling:

*Warnings.* (i) "Do not use if taking monoamine oxidase inhibitors. Discontinue use if dizziness, headache, fast pulse, tremors, or nervousness develop. Consult a physician if symptoms persist."

(ii) "Do not use this product if you have thyroid disease, high blood pressure, diabetes, or heart disease except under the advice and supervision of a physician."

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care decongestants. (See part VII. paragraph C. below—Data Required for Evaluation.)

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**Category III Labeling**

*Proposed indication.* "Aids in the temporaty relief of occasional discomfort due to congestion in the mouth and throat."

*C. Data Required for Evaluation*

The Panel agrees that the protocols recommended in this document for studies required to bring Category III drugs into Category I are in keeping with the present state of the sciences of pharmacology and therapeutics and the art of medicine and do not preclude the use of any advancements or improvements in methods for obtaining such data that might be developed in the future.

1. *General principles in the design of an experimental protocol for testing topical decongestant drugs.* The effects of decongestant drugs should be determined by their ability to reduce edema, dilation of capillaries and other vessels, and other manifestations of congestion of the buccal and pharyngeal mucous membranes in patients with acute or chronic stomatitis, or pharyngitis and other areas involving the mucous membranes in the mouth and throat. The Panel recognizes that there are no established protocols for testing the effectivenss of this category of product. The Panel suggests that the outline below be utilized unless the investigators have at their disposal alternate methods acceptable to the FDA. Tests should involve double-blind placebo-controlled assessment of a drug's ability to relieve the congestion. Topically applied nasal decongestants stimulate the alpha adrenergic receptors of the vessels in the mucosa and cause vasoconstriction. The normal pink color disappears, and the mucous membrane apears pale. Edema is reduced.

The Panel suggests that direct observation of the affected area be made by three independent observers after topical application of a drug by swabbing, spraying, or other methods in the proposed dosage. Precautions must be taken to avoid swallowing, because that would result in both a systemic effect as well as a local effect. Subjective assessment by the patient of the effect of the drug on symptoms present is also desirable and should be recorded. The drug should be the same as that present in the OTC preparation. It should be applied in the same dosage or concentrations as indicated on the labeling and in the same manner as that recommended in the label concerning instructions for use of the preparation. Since topical decongestants may be administered repeatedly during episodes of congestion, studies should be conducted over the appropriate time intervals recommended for dosing to maintain optimal relief of symptoms. When testing locally applied decongestants in which rebound congestion may follow repeated use, the effect of the drug must be allowed to "wear off" and observations made to note if rebound occurs. When rebound is of concern, labeling should specify that the product is for short-term use and provides only temporary relief of congestion. Specific data should be obtained by testing the topical decongestant effect in the usual recommended concentrations and also at the maximum dosage frequencies recommended for periods of at least 1 week, in order to assess the incidence of severity of drug-induced rebound congestion and possibility of sensitization. Absorption of the decongestant may occur through the mucous membranes in sufficient quantities to produce a pressor effect. Blood pressure and pulse rate should be monitored during the testing.

2. *Selection of patients.* Selection of patients for testing should be based on the diagnosis of stomatitis or pharyngitis with congestion. Patients should be grouped according to the similarity of the lesions and comparisons made between members of each group. The cross-over technique may be used for patients with chronic congestion, and they can serve as their own controls. Patients with acute infections may be studied, but the cross-over technique is not feasible because of the relatively brief course of acute disorders and the greater variation in the nature of the congestion that may be encountered. Larger numbers of these patients will have to be studied than with the cross-over group. They should be assigned in random fashion to placebo or drug groups. For comparative purposes, these groups must be matched by age, sex, and, if possible, the degree of congestion at the time of study. Smoking by test subjects should be prohibited 24 hours prior to and during the testing.

3. *Method of study.* Observations should include both subjective responses reported by the patient as well as objective data obtained by observing the congested area. If necessary and feasible, sequential colored photographs may be made for comparison before a placebo or drug is administered and at appropriate time intervals therafter to demonstrate onset, magnitude, and duration of the response. In testing the effect of decongestants upon the mucosa of the nasal passage, improvements in airflow and decrease in airway resistance are used as criteria of effectiveness of the drug in relieving congestion. The Panel suggests that such criteria may also be used for the mouth and throat in cases where the airway is compromised and the decongestant is responsible for an improvement.

4. *Interpretation of the data.* A recommended dose of the test drug should induce a statistically significant reduction in mucosal congestion when compared with a placebo response.

Evidence of drug effectiveness is required for a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to FDA must present both favorable and unfavorable results.

5. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing as outlined elsewhere in this document. (See part II. paragraph C.2.d. above—Safety evaluation.)

## VIII. Demulcents

### A. General Discussion

1. *General comments.* The following discussion of demulcents is based on a review of several sources (Refs. 1 through 4).

Demulcents are mucilaginous substances composed of gum, mucilages, starches, high molecular weight polyners of polyhydric alcohols and esters of polyhdric alcohols, polysaccharides, certain saccharides, and related colloidal materials. They form viscous solutions in water and a cohesive, protective film when applied to surfaces such as the skin or mucous membranes.

a. *Mode of action.* Demulcents are pharmacologically inert and nonreactive with tissue cell components. Their therapeutic usefulness is due to the fact that they protect the surface mechanically. They induce no changes in the cells with which they come in contact. When used for such purposes they are classed as active ingredients on the labeling. When applied to an inflamed, ulcerated, or otherwise sensitive cell surface, they retard movement or access of various chemicals, fluids, or air, and protect the surface from noxious stimuli produced by these agents. Some demulcents possess active adsorbing power and prevent noxious agents from sensitizing an irritated surface.

b. *Use of demulcents.* Demulcents may allay inflammation mucous membranes, especially those of the mouth and throat, by acting as protectants from chemicals and irritating stimuli. The effects are strictly local and due to physical rather than chemical action. Gums and other mucilaginous materials applied to a surface may exert a protective action against an irritant or poison. They may also be precipitant chemical antidotes for salts of heavy metals and other toxic substances. Demulcents are also used to emulsify oils, to suspend insoluble powders, and to delay the aborption of drugs. When used for this purpose, they are designated as pharmaceutical necessities and not as active ingredients. When used as pharmaceutical necessities, they are classed as inert ingredients on the labeling.

Mucilages and similar drugs derived from polysaccarides were formerly considered carbohydrate nutrients, but it has been shown that they are imperfectly digested and for the most part are absorbed and eliminated unchanged. Films of demulcents diminish the characteristic taste of many substances, such as acids, salts, and sweets as well as those that are bitter. They act by enveloping the substance and forming a protective layer over the mucous membrane. In this way they prevent access of the substance to the taste buds. In the case of acids, they act chiefly by adsorbing the acid on the surface of the colloidal particles. The acidic taste is minimized due to the decrease in concentration of the free form.

Demulcents interfere with the perception of various sensations such as cold, warmth, pressure, burning, or pain by protecting the receptors that mediate these sensations from agents that produce these stimuli. They exert no depressant effect on these receptors. They do not exert any anesthetic effect.

Among the numerous substances that have been used as demulcents are starch, gelatin, acacia, pectin, etc. When starch and gelatin are boiled with water, they undergo hydration and polymerization and become hydrophilic colloids. Gelatin forms a gel, and starch forms a paste. Acacia is a dry, gummy exudate derived from *Acacia senegal.* It forms a gummy viscous mass when dissolved in water, which acts as a demulcent on mucous membranes.

In essence, demulcents are protectants. Protectants are designed to cover the surface of a mucous membrane in order to prevent contact with irritants or noxious stimuli. Some protectants are powders that are in a very fine state of subdivision. They are used for dusting to form a coating over a lesion. Some demulcents form a semirigid fine coat when applied to a surface. Collodion, gelatin, methyl cellulose, and similar semiplastic material have been used on the skin and mucous membranes for this purpose. Attempts to use such substances on the mucous membranes have met with less success than on the skin.

Demulcents act as a barrier between the external environment and the surface of the mucous membranes. In addition they provide some mechanical support, which is a therapeutic advantage. They are more useful in this respect in preparations used on the skin rather than on the mucous membranes.

c. *Absorption of demulcents.* Most demulcents are inert and not absorbed. If absorbed, they are metabolized slowly or not at all. Demulcents are generally used in combination with other active ingredients. Some demulcents used on the mucous membranes of the mouth and throat form films for a short period of time because they are washed away by the saliva and swallowed and are therefore more useful than others that form persistent films. Demulcents applied to ulcerated surfaces or wounds on the mucous membranes of the mouth and throat fill depressions on these surfaces and thus remain in contact for a longer period of time than they do on the uninjured, healthy mucous membranes.

d. *Adverse reactions.* Demulcents do not cause serious adverse reactions because they are inert, nonirritating, and as a rule not haptenogenic. Demulcents obtained from biological sources that contain proteins and that may have not been purified can act as antigens.

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### B. Categorization of Data

1. *Category I conditions under which demulcent active ingredients for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

#### Category I Active Ingredients

Elm bark
Gelatin
Glycerin
Pectin

a. *Elm bark.* The Panel concludes that elm bark is safe and effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Elm bark (slippery elm) is the dried inner bark of *Ulmus rubra* (Refs. 1 and 2). The tree itself is indigenous to the United States and Canada. In the spring the old bark is stripped from the trees, and some of the outer and all of the inner part is removed. It is this inner part that is used for therapeutic purposes (Ref. 3). The bark has a currylike odor. Elm bark contains mucilaginous substances which are readily extractable by water. Elm mucilage consists principally of a polysaccharide which on hydrolysis yields D-galactose, D-methyl galactose, L-rhamnose, and glucose. Elm also

contains traces of tannin, which exerts no significant pharmacologic or therapeutic effect. Elm bark also contains some starch and traces of oxalate salts. The total ash content is approximately 7 to 10 percent. A warm infusion prepared by boiling the bark in water was a folk remedy used in the treatment of cough and diarrhea. The bark was also used as a poultice to treat external inflammation (Refs. 1, 4, and 5).

(1) *Safety.* The Panel concludes that elm bark is safe as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Little data were available in the literature or were provided in the submissions to the Panel concerning acute and chronic studies using elm bark in animals or in man (Ref. 6).

Elm bark is composed of polysaccharides that yield various innocuous sugars, and there have been no reports of adverse effects. It has enjoyed long-term use, and the Panel had judged elm bark to be a safe ingredient when used as a demulcent to treat symptoms of sore throat or sore mouth or both.

Elm bark was an official drug that was listed in the "United States Pharmacopeia" from 1820 to 1936 and in the "National Formulary" from 1963 until recently.

(2) *Effectiveness.* The Panel concludes that elm bark is an effective OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Ground elm bark yields a thick mucilage when digested in approximately 40 parts of cold water and incorporated into troches and lozenges. The mucilage rapidly forms a protective barrier over irritated and inflamed mucous membranes (Ref. 7).

There is no evidence that elm bark exerts any curative effects or promotes healing of lesions of the mucous membranes of the mouth and throat. Elm bark does not exert any anesthetic effect. Elm bark aids in the temporary relief of minor irritation or soreness of the mouth and throat (Ref. 6).

(3) *Dosage.* Adults and children 3 years of age and older: Use a 10.0- to 15.0-percent concentration of elm bark, incorporated in an agar or other water-soluble gum base, in the form of a lozenge every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

**References**

(1) Stecher, P. G., editor, "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 400, 1960.

(2) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 193, 1947.

(3) Youngken, H. W., "Drugs of Vegetable Origin," *in* "The Textbook of Pharmacognosy," 5th Ed., The Blakiston Co., Philadelphia, p. 272, 1943.

(4) Pratt, R., and H. W. Youngken, "Agents with a Physical Basis of Action," *in* "Pharmacognosy: The Study of Natural Drug Substances and Certain Allied Products," 2d Ed., J. B. Lippincott Co., Philadelphia, pp. 107–109, 1956.

(5) Trease, G. E., and W. C. Evans, "Pharmacognosy," 10th Ed., Williams and Wilkins, Baltimore, pp. 366–367, 1972.

(6) OTC Volume 130002.

(7) Wood, H. C., et al., "The Dispensatory of the United States of America," 23d Ed., J. B. Lippincott Co., Philadelphia, pp. 1186–1188, 1943.

b. *Gelatin.* The Panel concludes that geletin is safe and effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Gelatin is a protein obtained by the partial hydrolysis of collagen derived from skinlike and other connective tissues and bones of animals. Gelatin may be derived from acid- or basic-treated precursors. When derived from an acid-treated precursor, the gelatin is known as Type A; when derived from a basic-treated precursor, it is known as Type B. Type A gelatin has an isoelectric point between PH 7.7 and 9.0; Type B has an isoelectric point between PH 4.7 and 5.0 (Ref. 1).

Gelatin is available in sheets, flakes, shreds, or as a coarse fine powder (Ref. 1). It is faintly yellow or amber with a slight bouillonlike odor and is almost insolube in cold water. When immersed in water it gradually swells, due to its hydrophilic properties, and softens to form a colloidal solution having varying degrees of viscosity. Thus, gelatin solutions are referred to as hydrophilic colloids. The viscosity of gelatin solutions decreases with increases of temperature. Dry gelatin can absorb 5 to 10 times its weight of water. It is readily soluble in hot water, but is insoluble in alcohol, chloroform, and ether.

Gelatin is used as a demulcent on the mucous membranes of the mouth, throat, and stomach. Gelatin also has many uses as a pharmaceutical nesessity such as in the preparation of jellies, suppositories, and for suspension of drugs and in the preparation of troches (Refs. 1 and 2).

(1) *Safety.* The Panel concludes that gelatin is safe as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Gelatin is easily digested and used as a food as well as for medicines. Gelatin has been used as an adjuvant protein food, but is not a complete protein because it lacks certain essential amino acids, especially tryptophan. It cannot be used as a "complete" protein food unless it is combined with other proteins (Ref. 3).

The protective colloidal action of gelatin has been utilized in preparing modified milk formulas for infants. One to 2 percent gelatin lowers the curd tension of cow's milk. Gelatin solutions are amphoteric. This action makes them valuable as a food in cases of hyperacidic gastric states or in cases of peptic ulcer and other similar conditions because they can combine with acids by virtue of the amino groups on the amino acid molecules in the proteins.

The intravenous injection of gelatin solution greatly accelerates the ability of the blood to coagulate, and for this reason gelatin solutions were once used to treat internal hemorrhages (Ref. 3). Solutions of gelatin are difficult to sterilize, and unless the gelatin is absolutely pure, antigenic substances may be present and anaphylactic reactions may occur if administered intravenously. Gelatin is not a sensitizer when used topically and is devoid of any tendency to cause irritancy.

(2) *Effectiveness.* The Panel concludes that gelatin is effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Gelatin provides a protective coating over irritated or ulcerated areas of the mouth and throat and prevents stimulation of receptors for cold, warmth, pressure, or pain by protecting these receptors in distant areas from stimulation by physical or chemical agents. There is no evidence that gelatin exerts any curative effect or promotes healing of lesions of the mouth or throat.

A special form of gelatin, known as absorbable gelatin sponge, may be used on mucous membranes. It is a sterile, absorbable, water-insoluble gelatin base sponge made by bubbling or agitating a solution of partially denatured gelatin with air and drying the foam in an oven.

Gelatin is carried away by the saliva and swallowed, making its effect only short-lived when applied to healthy

mucous membranes. Gelatin does not undergo digestion in the mouth since there are no proteolytic enzymes in the saliva.

Gelatin, by its protectant action, aids merely in the temporary relief of pain and discomfort due to sore throat and sore mouth. Gelatin is not an anesthetic. Any relief of discomfort it affords is due to its protectant effects.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 5.0- to 10.0-percent concentration of gelatin in aqueous solution in the form of a rinse, gargle, spray, or by swabbing with an applicator or by applying digitally, as often as necessary. As lozenges or gels, use quantities sufficient to form a solid or semisolid state, as often as necessary. For children under 3 years of age there is no recommended dosage except under the advice of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

**References**

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 544, 1973.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 564, 1976.

(3) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 56–60, 1957.

c. *Glycerin.* The Panel concludes that glycerin is safe and effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Glycerin is a trihydric alcohol. It is also known as 1,2,3-propanetriol, glycerol, and trihydroxy-propane (Ref. 1). Glycerin was discovered by Scheele in 1779 in fats from which glycerin may be released by hydrolysis. It is the alcohol that esterifies the oils and fats of plant and animal origin. Glycerin is a clear, colorless, viscous, hygroscopic liquid with a sweet taste and characteristic odor (Ref. 2). It is miscible with water and alcohol and insoluble in chloroform and fixed and volatile oils. Glycerin is markedly hygroscopic and takes up and retains water in its undiluted form. Next to water, it is probably the most widely used vehicle for medicinal substances for internal or external use. In addition to glycerin's solvent properties, its value as a vehicle depends on its viscosity, its water-absorbing property, its ability to lower the surface tension of water, its osmotic effect, and its ready miscibility with water and alcohol. The inclusion of glycerin in many medicinal preparations that contain water, retards the hydrolytic decomposition of some active ingredients. Solutions of medicinal substances in glycerin are called glycerites (Ref. 3). In addition, glycerin is valuable as a preservative in liquid dosage forms containing sugar because it is nonfermentable. Glycerin is said to have antimicrobial properties due to its dehydrating and desiccating effects. Its antiseptic action, however, is of no particular consequence as far as this Panel is concerned because it is not used for this purpose on the mucous membranes of the mouth and throat. It is ineffective unless it is present in sufficient concentrations to dehydrate bacteria (Ref. 4).

Glycerin is used to alter the viscosity and other physical properties of medicinal products. It acts as a sweetening agent and as a vehicle for drugs used in or about the mouth or in the throat. Glycerin is widely used in the preparation of rinses and mouthwashes, and it helps maintain the consistency of toothpastes (Ref. 5).

Anhydrous and concentrated glycerin causes irritation when applied to the mucous membranes because its hygroscopic property may cause desiccation of tissues. This osmotic effect is also partially responsible for the laxative action of glycerin suppositories (Ref. 6). When glycerin is used in dermatological preparations, it exerts an emollient effect. Glycerin is also classified as a pharmaceutical necessity (Ref. 2).

(1) *Safety.* The Panel concludes that glycerin is safe as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Long-term clinical use and extensive marketing experience have confirmed that glycerin is safe for internal use. Glycerin has been used over 100 years as a medicament. When injected intravenously glycerin causes crenation of the red blood cells due to its osmotic effect, and hemolysis and hemoglobinuria result. Toxicity after oral administration has not been reported.

Glycerin is innocuous when taken internally. It has been ingested by adults in 100-g doses for 50 days with no ill effects (Ref. 7). Diarrhea may occur following massive oral doses, due to its osmotic effects. Undiluted glycerin has been applied to the conjunctiva of rabbits, rats, and dogs with no grossly visible ill effects. Undiluted glycerin has also been applied to the buccal mucosa of rabbits, rats, and dogs without any visible adverse local effects. However, glycerin absorbs water and can be dehydrating and irritating to the mucous membranes, particularly if inflamed. When used undiluted it may absorb water from ulcerations and open wounds and produce pain, burning, or other manifestations of irritation. Aqueous solutions of glycerin are nonirritating and act as safe protectants to the mucous membranes and skin.

Glycerin is nonantigenic. Reports of systemic sensitization are virtually nonexistent. Irritation of the mucous membranes may occur from the hygroscopic properties when used undiluted. Local sensitization and local allergic reactions have not been reported and apparently do not occur.

(2) *Effectiveness.* The Panel concludes that glycerin is effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Glycerin acts as a demulcent when applied to the mucous membranes of the mouth and throat. It coats the mucous membranes with a thin adherent film. Glycerin provides a protective coating over irritated or ulcerated areas of the mouth and throat and prevents stimulation of receptors for cold, warmth, pressure, or pain by protecting these receptors in diseased areas from stimulation by physical or chemical agents. There is no evidence that glycerin exerts any curative effect or promotes healing of lesions of the mouth or throat.

Concentrated glycerin absorbs water from tissues so that its soothing action is often preceded by smarting until it becomes diluted. It should, therefore, be diluted with two or three volumes of water or half a volume of 70 percent alcohol rather than used alone. This not only decreases its viscosity so that it is more easily applied, but also decreases its hygroscopic activity and desiccating effects (Ref. 8). Glycerin is absorbed from the mucous membranes. It is transported to the liver and transformed, to a certain degree, into glycogen and sugar.

Concentrations of 25 percent or more of glycerin manifest antimicrobial activity and are antiseptic due to its dehydrating effect. Undiluted glycerin destroys one tenth of the bacteria with which it comes in contact in 3 hours. It is not, however, useful as an antimicrobial agent. Glycerin allegedly increases the antimicrobial activity of phenol, thymol, and other antimicrobial agents (Ref. 8).

Glycerin, diluted with water, is indicated as a demulcent to aid in the temporary relief of minor irritations and

soreness of the mucous membranes of the mouth and throat. Glycerin manifests no anesthetic properties.

(3) *Dosage.* Adults and children 3 years of age and older: Use glycerin diluted with 2 or 3 volumes of water in the form of a rinse, mouthwash, spray, or by swabbing, as often as necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care demulcent active ingredients. (See part VIII. paragraph B.1 below—Category I Labeling.)

In addition, the Panel recommends the following specific labeling: "*Warning.* Do not use full strength. Dilute with two or three volumes of water."

**References**

(1) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 1254–1255, 1975.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 581, 1976.

(3) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 196, 1947.

(4) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 116–117, 1965.

(5) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, pp. 245–246, 1977.

(6) "United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, p. 223, 1975.

(7) Deichman, W., "Glycerol—Behavior in the Animal Organism (A Review of the Literature)," *Industrial Medicine,* 9:60–67, 1940.

(8) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 127–128, 1957.

d. *Pectin.* The Panel concludes that pectin is safe and effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Pectin is a polysaccharide consisting chiefly or partially of polymerized methoxylated polygalacturonic acid molecules (Ref. 1). Pectin is obtained from the inner portion of the rind of citrus fruits, apples, and other botanical sources. The greater portion of pectin in fruit is present in a form known as propectin. Propectin is insoluble in water. This is converted into water soluble pectin by heating with a weak acid. The resulting product is purified by precipitating with alcohol or salting out with electrolytes.

Pectin is a mixture of polysaccharide molecules of various sizes. Pectin is not a single entity compound. Pectin is a coarse or fine yellowish-white powder (Ref. 2). It is soluble in 20 parts of water forming a viscous, opalescent, freely flowing colloidal solution. Pectin is insoluble in concentrated or diluted alcohol and other organic solvents.

The pectin molecules are large molecules of varying sizes. The molecular weights range between 150,000 and 300,000 daltons. It is composed of galacturonic acid anhydride molecules, some of which are partially methoxylated. Three carboxyl groups are present on each molecule of pectin. Some of these are esterified. The carboxyl groups impart acid properties to the molecule. Pectin forms gels which may be standardized to "150 jelly grade" by addition of dextrose or other sugars. Pectin may contain sodium citrate or other buffering agents. The viscosity and jelly strength of pectin depend primarily on the size of the molecules while the degree of methoxylation affects the setting time, reactivity with metallic ions, and other such characteristics. Certain nongalacturonide components, such as galactan and araban, may constitute one-third or more of pectin and may also modify its characteristics (Ref. 3).

(1) *Safety.* The Panel concludes that pectin is safe as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit ser forth below.

Pectin has been used in foods for jellies and medicinally as a demulcent and a pharmaceutical necessity. Pectin has been combined with kaolin and used as a protective agent for treating diarrhea (Ref. 4). An aquesous suspension consisting of 20 percent pectin and alpha kaolin is used as an intestinal adsorbent (Ref. 5). In the diet, pectin allegedly causes a lowering of serum cholesterol levels. The Panel does not consider this to be of any significane clinically if used occasionally, topically, and in limited quantities on the mucous membranes of the mouth and throat. Pectin solutions of an approximate 1-percent concentration were once used as plasma volume expanders in the treatment of hemorrhage and shock (Ref. 5). Pectin is no longer used for this purpose. It is retained and causes degenerative changes in the tissues.

Pectin has no adverse effects on the skin or mucous membranes. It is not irritating and nonantigenic. Sensitization has not been known to occur following topical application.

(2) *Effectiveness.* The Panel concludes that pectin is effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

When suspended in water, pectin forms a sol containing negatively charged, highly hydrated particles. Pectin is strongly hydrophilic.

Pectin is nearly neutral in reaction and is amphoteric, as are proteins. Pectin is more stable in acid than in alkaline media. In the presence of alkalies the methyl groups forming the esters are saponified and the glycosidic linkages that bind the glacturonic acid units may be disrupted and render the compound ineffective. Nongalacturonide components, such as galactan and araban, normally present in pectin may modify its characteristics when present in a proportion of one-third or more of the total weight of pectin.

Pectin exerts no pharmacologic effect of its own except that it acts as a demulcent and a protectant. It forms a cohesive film that holds a drug in contact with an irritated, inflamed, or ulcerated mucous membrane. Pectin does not retard would healing. Pectin provides a protective coating over irritated or ulcerated areas of the mouth and throat and prevents stimulation of receptors for cold, warmth, pressure, or pain by protecting these receptors in diseased areas from stimulation by physical or chemical agents. There is no evidence that pectin exerts any curative effect or promotes healing of lesions of the mouth or throat. Pectin exerts no anesthetic effect. Relief of discomfort is due to its protectant effects.

The term "150 jelly grade" indicates that pectin will produce a jelly when 1 part is mixed with 150 parts of sugar in a medium containing a final concentration of 55 percent sugar adjusted to the desired acidity. Less viscous preparations may be prepared for use in the oral cavity as a gargle, a rinse, or for direct application by swabbing.

(3) *Dosage.* Adults and children 3 years of age and older: Use a solution of pectin of desired viscosity in the form of a rinse, gargle, spray, or by swabbing, as often as necessary. Use quantities sufficient to form a solid or semisolid state in the form of lozenges or gels, as often as necessary. For children under 3 years of age there is no recommended dosage except uder the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care demulcent

active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

**References**

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 845, 1973.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 915, 1976.

(3) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, p. 611, 1965.

(4) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 131, 1957.

(5) Swinyard, E. A., "Surface-Acting Drugs" *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 949, 1975.

(6) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 820, 1947.

**Category I Labeling**

a. *Indication.* "Aids in the temporary relief of minor discomfort and protects irritated areas in the mouth and throat."

b. *Warnings*—(1) *For all oral health care products containing demulcents.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For oral health care products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which demulcent active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral health care drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

*Category II Active Ingredients*

None.

**Category II Labeling**

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use or for description of product attributes for products containing oral health care demulcent active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowing for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "For relief of sore throat due to smoking."

(2) "Helps reduce minor oral inflammation."

(3) "Promotes healing."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Given quick relief."

(2) "Acts fast."

(3) "Produces a smooth coating that gives quick comfort to irritated throats."

c. *Statement or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Recommended by doctors."

(2) "Multiaction."

(3) "Superior new formulation."

(4) Adding such terms as "plus" etc.

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* (1) "First aid to throat irritation."

(2) "Works directly on throat membrane."

(3) "Soothes tired throats."

(4) "Fights sore throat."

e. *Statements or phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion the diagnosis of which must be made by a physician.*

(1) "To relieve discomfort due to stomatitis."

(2) "For relief of pain due to canker sores."

(3) "For relief of pain due to cold sores."

(4) "For relief of pain for minor sore throat due to common cold."

(5) "Relieves smokers sore throat."

(6) "Relieves pain due to tonsillitis."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom or disease state when proof that this occurs is lacking.* "Prevents dryness of mouth and throat."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "Hygienic prevention."

(2) "Relieves dryness."

(3) "Reduces mouth odors."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic or therapeutic action or class of a drug or type of formulation containing the ingredients instead of designating the symptoms which the product intended to relieve.* (1) "Demulcent."

(2) "Gargle."

(3) "Mouth rinse."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* None.

**IX. Expectorants**

*A. General Discussion*

1. *Introduction.* An expectorant is a substance that increases the output of respiratory tract fluid and promotes the expulsion of secretions from the lower and upper respiratory tract, mouth, or throat, thereby aiding in the relief of irritation or soreness of the mucous membranes of these structures. Expectorants are used to aid in the relief of symptoms due to inflammation or irritation in the lungs, bronchi, trachea, larynx, throat, and mouth. Expectorantia may actually be lifesaving when secretions are collecting in the larynx and trachea (in combination with other measures). Expectorants may indirectly facilitate the healing process by relieving these symptoms. There is no evidence that they have any direct action on the healing process.

a. *Mode of action.* Expectorants may act by one or a combination of the following mechanisms: (1) They may increase the volume of respiratory tract fluid. This results in a "thinning action" that facilitates removal of thick secretions resulting from a disease process in the mouth, throat, or respiratory tract. (2) They may promote the secretion of alkaline respiratory tract fluid in the bronchi, trachea, mouth, or throat. This reduces the viscosity of mucus and other secretions and debris in the mouth thereby facilitating their expulsion. They may reduce the viscosity of the secretions if volatilized and inhaled with steam and other propellants. This increases the secretory activity and increases expectoration. (3) They may act by promoting coughing, which mechanically dislodges the secretions in the lower respiratory tract and causes their expulsion. (4) They may stimulate the sensory endings of the vagus nerves, thereby causing an increase in watery secretion of the salivary glands and the mucous glands of the throat, esophagus,

stomach, and bronchi. This causes liquefaction and dissolution of thickened and viscous exudates and aids in the thinning of viscous mucus or purulent material in the upper air passengers or in the mouth and throat. (5) They may also increase salivation. By doing so they provide the antimicrobial activity of the saliva in addition to thinning secretions, etc.

Certain drugs, particularly those with cholinergic activity, promote the flow of saliva and are often referred to as sialogogues. Acids and small pieces of certain types of foods, such as pickles, may do likewise.

The secretions of the mucous membranes can be increased and made more fluid by various salts, such as ammonium chloride and potassium iodide. Potassium iodide increases output of various secretions, as is evident by the increase in lacrimal gland and nasal secretions in iodism. Secretions in the throat are also increased by potassium iodide.

Expectoration is actually a debriding process. There is, however, a distinct difference between expectorants and debriding agents. Expectorants Act endogenously and promote secretion of respiratory tract fluids. Debriding agents are substances that are added exogenously to mechanically assist in removal of debris from the mouth and throat.

b. *Uses of expectorants.* There is considerable doubt as to whether expectorants are of any therapeutic value. There is some evidence that expectorants may be effective in the lower respiratory tract. However, there is less evidence that expectorants are effective in the mouth and throat. Their effectiveness for relieving symptoms of sore throat or sore mouth has not been established with certainty. The term "expectorant" literally means "out of the chest," but it has been expanded to include some remedies that act in the throat. Some expectorants are excerted into the respiratory tract, throat, and mouth and act by local irritation. Expectorants acting by local irritation are termed "stimulant expectorants" because they stimulate the mucosa directly. Drug that promote expectorant activity by decreasing the viscosity of the mucus are called liquefying expectorants. Alkaline expectorants liquefy mucus by splitting the polysaccharide from mucoproteins. They may act above the larynx in the mouth and throat when used in a lozenge form. Most expectorants are swallowed.

c. *Adverse reactions.* Some expectorants in oral health care products may, if used to excess, be swallowded and cause gastric irritation. Iodides accumulate in the body and may cause iodism. Ammonium chloride may cause acidosis.

Expectorants may aggravate discomfort due to sore throat or sore mouth by inducing coughing if they increase the amount of lower respiratory tract fluid. Expectorants that cause local irritation may aggravate the symptoms of sore throat and sore mouth. Expectorants that are used systemically may be excreted in the saliva and cause a persistent, disagreeable taste which is unpleasant and may be irritating to lesions causing sore throat and sore mouth.

*B. Categorization of Data*

1. *Category I conditions under which expectorant active ingredients for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

**Category I Active Ingredients**

None.

**Category I Labeling**

a. *Indications.* The Panel did not classify any expectorant active ingredient in Category I, but did place some ingredients in Category III. Because additional testing is necessary to determine the actual effect these ingredients have in the mouth and throat, the Panel did not place any indication in Category I. The Panel has proposed a Category III indication for expectorants. (See part IX. paragraph B.3. below—Category III Labeling.)

b. *Warnings*—(1) *For all oral health care products.*

(i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For oral health care products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which expectorant active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral cavity expectorant drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

**Category II Active Ingredient**

Potassium iodide

*Potassium iodide.* The Panel concludes that potassium iodide is not safe and that there are insufficient data available to permit final classification of the effectiveness of potassium iodide as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium iodide is a colorless or white powder composed of cubical crystals or white granules. It is slightly deliquescent in moist air. Long exposure to light or moisture causes potassium iodide to become yellow due to liberation of iodine and small quantities of iodates. This can be prevented by the addition of small amounts of alkali. Aqueous solutions of potassium iodide are a colorless, odorless, neutral, or slightly alkaline (pH 7–9) liquid having a characteristically strong salty taste that can be masked by administering it in milk or various flavored syrups.

One gram of potassium iodide dissolves in 0.7 mL water, 0.5 mL boiling water, 22 mL alcohol, 8 mL boiling alcohol, 51 mL absolute alcohol, 8 mL menthol, 75 mL acetone, 2 mL glycerol, and about 2.5 mL glycol. Solutions of potassium iodide readily dissolve elemental iodine to form iodophors (Refs. 1 and 2).

Potassium iodide may be reduced to elemental iodide in the gastrointestinal tract. Both the elemental iodine and the salt are absorbed from all parts of the gastrointestinal tract. The kidney is the chief excretory organ for potassium iodide. Sixty-five to 80 percent of the iodide ion appears in the urine within 24 hours after the administration of a single dose of pottasium iodide. It is also found in tears, saliva, sebum, secretions from the nasal mucous membranes, sweat, feces, and milk (Refs. 3 and 4).

(1) *Safety.* The Panel concludes that potassium iodide is not safe as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium iodide, when used in doses considered to be therapeutically effective (300 mg every 4 to 6 hours) is not considered safe for use in OTC preparations. Although potassium iodide has been widely used in medical practice as an expectorant and for treating skin disorders and various other clinical conditions, adverse effects from its continued use are far from rare. The

action and toxic effects of potassium iodide are due to the iodide content.

Manifestations of toxicity due to iodides and iodine vary considerably not only in different individuals, but in the same individual at different times (Ref. 4). Side effects and toxic effects due to iodides are dose related. Iodism develops in practically all persons chronically treated with high doses of iodide compounds. However, some individuals are highly sensitive to iodides and react to the first few doses with serious symptoms (Ref. 5). Anaphylaxis and other allergic manifestations have been reported.

The commonest symptom of iodism is inflammation of the mucous membranes (catarrh) of the respiratory passages, especially the nose. Occasionally swelling, edema, and small ulcers in the larynx develop. Severe respiratory obstruction necessitating tracheotomy has been reported. Bronchitis has also been reported in humans following the use of potassium iodide. Profuse watery secretions often resulted in these cases. In animals, edema of the lungs and pleuritic effusions have followed the injection of iodides. Other symptoms of iodism include salivation, coryza, sneezing, conjunctivitis, headache, fever, laryngitis, stomatitis, parotitis (iodine mumps), various skin rashes (iododerma, thrombotic thrombocytopenic purpura), brassy taste, burning of the mouth and throat, chronic sore gums and teeth, and symptoms of a head cold may also result. Edema of the glottis, necessitating tracheotomy, has also been reported following the use of potassium iodide (Refs. 4 and 6).

Carswell, Kerr, and Hutchison (Ref. 7) reported iodide-induced goiters in the fetuses of pregnant women. Two cases of neonatal death, apparently resulting from congenital goiter caused by iodides compressing the trachea, were reported by Galina, Avnet, and Einhorn (Ref. 8). Continued excessive use of iodide in children and adults may produce goiter or hypothyroidism or both (Refs. 9 and 10). The "Medical Letter on Drugs and Therapeutics" (Ref. 11) discusses the hazards of drug-induced goiters and cites iodides as a frequent cause.

Iodides generally induce nausea and gastric discomfort. A single dose of potassium iodide increases the volume of gastric juice secreted and prolongs the elaboration of secretions aroused by the taste of food. Large quantities of iodides also cause irritation of the stomach due to a local salt action on the mucosa. Nausea, vomiting, and, more rarely, diarrhea result. These adverse reactions may occur with single doses and necessarily a manifestation of iodism.

Other adverse reactions have been reported by Shelly (Ref. 12). He discussed the systemic manifestations of two patients who had iodism. These included hepatitis, fever, leukocytosis, hypoproteinemia, hypocalcemia, and an elevation of serum transaminase and alkaline phosphatase. A challenge with 500 mg of orally administered potassium iodide reproduced a typical attack.

Skin eruptions occur frequently in iodism particularly after prolonged treatment. These eruptions may simulate almost all known skin diseases; however, the most common manifestations are erythematous patches, or papular eruptions. These may progress into pustules or into larger inflamed areas (Ref. 4).

Falliers et al. (Ref. 13) reportedly found a high incidence of adverse reactions in a double-blind crossover study of 52 asthmatic children on iodide therapy. One child developed a papulovesicular eruption, and treatment was discontinued. Sixteen adolescents developed acneiform lesions. Eighteen patients developed thyroid enlargement but no evidence of suppressed thyroid function. Leonardy (Ref. 14), in discussing the use of iodides in the treatment of bronchial asthma, cited a review by Peacock and Davison (Ref. 15) involvig 500 patients. In this series, 13.5 percent of the patients developed reactions of such severity that treatment was discontinued.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit the final classification of the effectiveness of potassium iodide as an OTC expectorant for topical use on the mucous membranes of the mouth and throat.

Although there is experimental evidence that indicates that potassium iodide increases the secretion of respiratory tract fluid (RTF), such evidence is from uncontrolled studies and is sparse and unconvincing. Thus, the therapeutic efficacy of potassium iodide is doubtful (Ref. 16). The presence of iodides in the RTF has been demonstrated in animals, but whether this increases the amount of RTF secreted or morely decreases its viscosity is not established (Refs. 17 and 18).

Potassium iodide is believed to increase bronchial secretions in the respiratory tract by reflex stimulation of the gastric mucosa. It is believed to act in the same manner as ammonium chloride. There are no data substantiating that this reflex stimulation causes an increase in the secretions from the glands of the mouth and throat. The use of the drug is limited by its unpleasant taste and frequency of adverse reactions.

Potassium iodide has been used as a gargle, in lozenges, troches, and "cough drops" presumably to stimulate the flow of saliva and to prevent the "drying out" of the pharyngeal mucosa.

Falliers et al. (Ref. 13), in a 3-year, double-blind study in 52 children with chronic asthma, using 300 mg, three times daily, demonstrated a statistically significant improvement in symptoms. Those receiving iodides improved, but there was a wide variation in the response. This study, however, does not lend any support to the effectiveness of potassium iodide used topically on the mucous membranes of the mouth and throat.

(3) *Evaluation.* The Panel concludes that potassium iodide is not safe and that there are insufficient data on its effectiveness as an OTC expectorant active ingredient for topical use in the mouth and throat.

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**Category II Labeling**

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use or for description of product attributes for products containing expectorant active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases that purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Temporary relief of sore throat due to the common cold."

(2) "Relieves stuffed up feeling."

(3) "Subdues cough reflex."

(4) "Relieves mouth and throat pain."

(5) "Works internally to break up phlegm."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general; nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Provides prompt relief of throat discomfort."

(2) "Rapidly relieves discomfort."

(3) "Fast relief."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with similar action.* (1) "Superior expectorant."

(2) "Improved formulation."

(3) Adding terms such as "plus" etc.

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* "Provides relief by local cleansing action."

e. *Statements or phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion, the diagnosis of which must be made by a physician.* "Healing aid for minor oral inflammations."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a disease state or symptom when proof that this occurs is lacking.* (1) "Soothing and cleansing to the mouth and throat."

(2) "Prevents infection."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes, but imply that a product exerts a therapeutic effect.* (1) "For mouth and gum care."

(2) "Promotes oral hygiene."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic or therapeutic action or class of a drug or type of formulation containing the ingredients instead of designating the symtoms which the product is intended to relieve.* (1) "Expectorant."

(2) "Promotes salivation."

(3) "Mouthwash."

(4) "Promotes needed expectoration."

3. *Catefory III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

**Category III Active Ingredients**

Ammonium chloride
Horehound
Tolu balsam

a. *Ammonium chloride.* The Panel concludes that ammonium chloride is safe, but that there are insufficient data available to permit final classification of the effectiveness of ammonium chloride as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Ammonium chloride is also known as muriate of ammonia and sal ammoniac. It occurs as colorless crystals, or a white, fine, or coarse crystalline powder. One gram of ammonium chloride is soluble in about 3 mL water, about 100 mL alcohol, about 8 mL glycerin, and about 1.4 mL boiling water (Ref. 1). Ammonium chloride has been used for many years as a medicinal agent.

(1) *Safety.* The Panel concludes that ammonium chloride is safe as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Clinical experience over many years of use has confirmed that the oral administration of ammonium chloride is safe when used in the dosage range recommended as an expectorant. The $LD_{50}$ in rats of ammonium chloride given intramuscularly is 30 mg/kg. There are no controlled clinical studies documenting the safety of the drug when used topically on the mucous membranes of the mouth and throat; however, its long-term clinical use attests to its safety.

There are numerous human studies documenting the occurrence of progressive hyperchloremic acidosis when ammonium chloride is used orally, especially in patients with renal, hepatic, or pulmonary insufficiency (Refs. 2 through 5). Most of these occurred with doses in excess of 6 to 8 g per day. The drug was formerly used as a diuretic for the treatment of heart failure. Relmane, Shelburne, and Talman (Ref. 6) reported two nearly fatal cases following the ingestion of excessive amounts (82 g in a 48-hour period). Ticktin, Fazekas, and Evans (Ref. 7) have described a case of hepatic coma precipitated by an 8-g dose of ammonium chloride in a patient with congestive heart failure. When the oral dosage range of 250 to 500 mg 4 to 6 times daily has been used, the customary dose for use as an expectorant, the most common adverse reactions have been nausea and in some cases vomiting (Ref. 8).

Ammonium chloride is rapidly absorbed from the gastrointestinal tract following oral administration. Complete absorption occurs within 3 to 6 hours. Oral administration of relatively large doses of ammonium chloride may induce nausea and vomiting (Ref. 9). In patients with renal insufficiency a progressive hyperchloremic acidosis occurs. In the presence of liver disease, it may cause ammonia intoxication similar to that occurring spontaneously in hepatic coma (Refs. 5 and 10).

After oral administration, some ammonium chloride is excreted unchanged into the urine, while some is converted to urea. Transformation to urea occurs in the liver and proceeds rapidly. The end products are urea and hydrochloric acid. The latter reduces the alkaline reserve in the blood, producing acidosis.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of ammonium chloride as an OTC expectorant active ingredient

for topical use on the mucous membranes of the mouth and throat.

The ammonium ion is believed to exert an expectorant action, and its salts are extensively used for this purpose (Refs. 11), but the evidence to support this contention is not convincing. However, the ammonium salts are rarely used alone but are used in combination with other ingredients (Ref. 5). The chloride is the salt most commonly prescribed for its effect on the respiratory mucous membranes and is a common constitutent of many expectorant mixtures (Ref. 12). The lozenge is often used for treating symptoms of sore throat. The salt is believed to exert its expectorant action by reflexly stimulating the vagal nerve endings in the mucosa of the stomach. Irritation of the gastric mucosa has been shown experimentally to cause an increase in secretion of respiratory tract fluid in the mouth, throat, larynx, trachea, and bronchi (Refs. 5, 10, 13, and 14). Of all the ammonium salts, the chloride appears to be the most effective for decreasing the viscosity and diminishing the tenacity of mucus. Following the administration of ammonium chloride, traces of ammonium carbonate are formed in the bronchial mucous membrane. This is alkaline and aids in liquefying the mucus; it also stimulates the ciliary movements which facilitate expectoration of mucus and debris resulting from a disease process (Ref. 15).

Goth (Ref. 13) states that a number of expectorants are believed to stimulate production of respiratory tract fluid by a reflex action arising from vagal sensory nerve endings of the stomach. Ammonium chloride was one drug studied, but proof of effectiveness is lacking. "AMA Drug Evaluations" (Ref. 5) states that the therapeutic efficacy of ammonium chloride as an expectorant is doubtful. Evidence of effectiveness is sparse and unconvincing.

Cushny (Ref. 12) states that "ammonium chloride can be credited with rendering the mucus secretion of the stomach and bronchi more abundant and less tenacious." No data are offered in support of the contention.

The use of expectorants, including ammonium chloride, appears to be based more on tradition and the widespread clinical impression that they are effective rather than on sound scientific proof (Ref. 5). The Panel believes that ammonium chloride plays an insignificant role in the mouth and throat in the removal of secretions. The effectiveness of ammonium chloride, despite its widespread and long-time use, remains in doubt.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use up to 150 mg of ammonium chloride in the form of a cough syrup not more than three to four times daily. Use a lozenge containing up to 150 mg of ammonium chloride every 2 hours if necessary. For children under 3 years of age, there is not recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care expectorant active ingredients. (See part IX. paragraph B. 1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care expectorant active ingredients. (See part IX. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care expectorants. See part IX. paragraph C. below—Data Required for Evaluation.)

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b. *Horehound.* The Panel concludes that horehound is safe, but that there are insufficient data to permit final classification of the effectiveness of horehound as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Horehound is an old-time medicine of botanical origin. Horehound (*Marrubium vulgare*) is also known as hoarhound, gypsy wart, harbane, and madwort (Ref. 1). It was official in the "United States Pharmacopeia" from 1820 to 1916 (Ref. 2).

The plant from which horehound is obtained is native to Europe, North Africa, and Western Asia. It has been cultivated in North America. Horehound is a mixture containing a volatile oil, resin, tannin, and a crystalline bitter principle called *Marrubiin.* It has an aromatic odor and a persistent bitter taste (Ref. 1). Hollis, Richards, and Robertson (Ref. 3), concluded that the active ingredient in horehound is a hydroditerpine lactone, whose empirical chemical formula is $C_{21}H_{28}O_4$. The molecular weight of the compound is 344.43. The crystals melt between 150 and 160° F. Horehound is slightly soluble in water, and soluble in alcohol, chloroform, ether, pyridine, phenol, and petrol ether (Ref. 2).

Horehound was once used as a domestic remedy for the treatment of colds and coughs. Earliest documentation of medicinal use cited by Bickerman (Ref. 4) dates back to a 16th century treatise on cough remedies in which horehound was mentioned along with other drugs as a "spurge through the sputa."

Horehound is classed as a stimulant, a diaphoretic, a laxative, and a diuretic (Refs. 2, 5, and 6). Horehound was formerly used as an aromatic,

stomachic, and an expectorant in various forms of bronchitis. Pages and Comte (Ref. 7) reported obtaining beneficial results in the treatment of cardiac extrasystoles using an extract of fresh horehound. The dried plant is of little clinical value.

Horehound was given in the form of a hot infusion, also called a "tea," or as a tincture for its stimulant and diaphoretic effects. The beneficial effects obtained from the use of these old fashioned remedies lie perhaps more in the large draughts of warm water rather than in the traces of volatile oil that they contained. The oil presumably prevents, to some extent, the nausea produced by the warm water alone (Ref. 6). The infusion or tincture can be given cold. It is a bitter tonic once used to treat coughs due to tuberculosis. It was also used as an expectorant in syrups.

Horehound in fusions, or tinctures in hot water sweetened with honey were reported to be beneficial for use in asthma and for treating various inflammations of the lungs and bronchial tubes. A syrup was prepared with honey and kept on hand in many households to loosen phlegm and relieve discomfort caused by coughs and colds (Ref. 5).

When treating deep-seated colds with coughs, horehound was combined with tincture of sculecap (*Scutellaria laterfolia*) and tincture of pleurisy root (*Ascelpias tuberosa*). The combination was administered in warm water.

Horehound in combination with peppermint and spearmint was used for colic and cramps. This combination was also administered in hot water and given as frequently as necessary (Ref. 5).

The above historical account of the use of horehound for treating respiratory infections is of interest, but its widespread use was based upon tradition or clinical impression. No data from controlled studies are mentioned in any of these citations.

(1) *Safety.* The Panel concludes that horehound is safe as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

No data are available on the animal and human toxicity of horehound. Adverse effects or cases of poisoning have not been reported despite the fact that it has been used as a medicinal since the 16th century (Ref. 5).

On the basis of long-term use and experience the Panel concludes horehound is safe for OTC use on the mucous membranes of the mouth and throat.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of horehound as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

One text states that horehound, given orally, was formerly used as an expectorant in various forms of bronchitis, but its use has since "been abandoned by physicians." Another text states that it was dropped from the "Primary List" of drugs in 1910 (Ref. 8). Verbon, as cited by Clymer (Ref. 5), claims that "horehound is an effective expectorant and stimulant in 'breaking up' recent colds, bronchitis, bronchial catarrh, and certain types of asthma where the mucous expectoration can relieve dyspnea, aphonia, and laryngitis." No data from controlled studies are supplied in support of the contention.

The use of expectorants, including horehound, appears to be based more on tradition and the widespread clinical impression that they are effective, rather than on sound scientific proof. The Panel concludes that horehound plays an insignificant role in the mouth and throat in the removal of secretions. The effectiveness of horehound, despite its widespread and long-time use, remains in doubt.

The Panel feels that the available data on the expectorant effects of horehound are insufficient to make an evaluation and that additional data are necessary before it can be classified as a Category I expectorant active ingredient.

(3) *Proposed dosage.* Adults and children 3 years of age and older: For the herb, mix 1 tablespoonful of the herb into 1 or 2 cupfuls of water. Take this mixture orally every 2 to 3 hours. For the tincture, alone, add 20 to 30 drops to water and take this mixture orally ever 2 to 3 hours.

In using an infusion or "tea," 1 tablespoonful of herb is added to a cup of boiling water. Let this steep for half an hour. One tablespoonful, sweetened with honey, is administered as frequently as necessary.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care expectorants active ingredients. (See part IX. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care expectorant active ingredient. (See part IX. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care expectorants. (See part IX. paragraph C. below—Data Required for Evaluation.)

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c. *Tolu balsam.* The Panel concludes that tolu balsam (balsam of tolu, tolu preparations, tolu balsam tincture) is safe, but that there are insufficient data available to permit final classification of the effectiveness of tolu balsam as an effective OTC expectorant active ingredient for use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Tolu balsam is an exudate obtained from *Myroxylon balsamum* (linne), a South American tree. Balsams are naturally occurring mixtures of resins, volatile oils, and organic acids. Tolu balsam contains from 12 to 14 percent free cinnamic and benzoic acids, approximately 40 percent benzyl esters of these acids, and approximately 1.5 to 3 percent volatile oils. It is a yellow-brown, semisolid fluid that has an aromatic odor and taste. Tolu balsam is insoluble in water and soluble in alcohol, benzene, chloroform, ether, and almost insoluble in petroleum ether (Refs. 1 and 2).

(1) *Safety.* The Panel concludes that tolu balsam is safe as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Balsams have been used since antiquity for medicinal purposes. Tolu balsam is a feeble expectorant and has

been used in cough mixtures for many years. It has been administered in oral doses of 0.6 to 2 g. It is used as a tincture, as well as alone as the balsam. Tolu balsam syrup is employed as a vehicle for expectorant drugs, but it has no specific value for this purpose. Tolu balsam has been used in the treatment of tuberculosis, but it is worthless for this purpose (Ref. 2). Tolu balsam has been used by injection, apparently without any harmful effects. There are no animal and human toxicity data available, but it is not considered to have any degree of toxicity (Ref. 3). The toxicity rating, according to Gosselin (Ref. 4), is 3. Balsam tolu syrup has been included in the "National Formulary." It is no longer mentioned in any of the official compendia, the last being the 14th Edition of the "National Formulary" and the 1975 "U. S. Pharmacopeia."

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of tolu balsam as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth or throat when used within the proposed dosage limit set forth below.

Tolu balsam has been employed occasionally in the treatment of contaminated wounds for its stimulating and mild antiseptic action. It has also been used in the treatment of scabies, as an expectorant in inhalant mixtures for chronic bronchitis, and for the reduction of secretions. The Panel finds no reference to the use of tolu balsam as an expectorant in the teatment of lesions of the mouth or for treating sore throat or other afflictions of the throat (Ref. 2).

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use 0.6 to 2.0 g of tolu balsam per dose in the form of rinses, mouthwashes, sprays, or drops, not more than three to four times daily. Use a lozenge containing 0.6 to 2.0 g of tolu balsam every 2 hours if necessary. For children under 3 years of age there is no recommended dosage except under the supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care expectorant active ingredients. (See part IX. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care expectorant active ingredients. (See part IX. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care expectorants. (see part IX. paragraph C. below—Data Required for Evaluation.)

**References**

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 126, 1976.

(2) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 1440, 1955.

(3) Boyd, E. M., "Expectorants and Respiratory Tract Fluids," Pharamacological Reviews, 6:521–542, 1954.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 156, 1976.

**Category III Labeling**

*Proposed indication.* "Aids in the removal of secretions and in the temporary relief of discomfort due to occasional sore throat and sore mouth."

*C. Data Required for Evaluation*

The Panel agrees that the protocols recommended in this document for studies required to bring a Category III drug into Category I are in keeping with the present state of the sciences of pharmacology and therapeutics and the art of medicine and do not preclude the use of any advancements or improvements in methods for obtaining data that might be developed in the future.

1. *General principles in the design of an experimental protocol for testing expectorant drugs.* The effectiveness of a topically applied expectorant is based on its ability to increase the flow of low-viscosity fluid from the salivary and other exocrine glands in the mouth and throat in order to facilitate the removal of inspissated sputum, cellular debris, purulent, and other matter from the mouth and the buccal cavity. Such purulent matter, secretions, and cellular debris often act as foreign bodies on a diseased or otherwise afflicted area and induce stimuli that cause pain and discomfort. Their presence may interfere with the normal spontaneous resolution of a disease process and interfere with healing. By aiding in the removal of such debris and secretions from irritated or ulcerated mucous membranes, expectorants may indirectly ease discomfort due to inflammatory or other pathologic processes. Determination of the increased volume of secretions induced by a topically applied expectorant is not as simple as it would seem. There are no established protocols for testing this category of product. There are no suitable objective methods for making such evaluations. This difficulty stems partly from a lack of basic knowledge concerning the biochemical and physiochemical nature of secretions in pathologic states involving the mouth and throat, as well as changes produced by expectorant drugs. It also stems from lack of knowledge concerning which property of the sputum and other fluids secreted into the mouth and throat correlates best with the ease of expectorant activity.

The volume of fluid secreted in the mouth and throat could be measured using volunteers as subjects. The subject could expectorate the secretions into a receptacle for a selected period of time and the volume, color, viscosity, density, pH, and other chemical and physical characteristics noted to obtain baseline or control data. The drug should be applied as proposed in the labeling and the subject told not to swallow. After the proper time interval necessary for the drug to act has elapsed, the subject could expectorate at selected intervals into a container and the volume, viscosity, and appearance of the fluid observed; the change in volume and other parameters resulting from the drug's action could be compared with those noted in the control. Trotti and Adriani (Ref. 1) measured secretory activity of the buccal glands and the salivary glands by applying strips of pure cotton that had been previously weighed, in the oral cavity between the cheek and the gingiva. The cotton absorbed the secreted fluids. These cotton strips were removed after 15 minutes and the gain in weight was determined to obtain the control value of normally secreted fluid. The process was repeated at 15 minute intervals after administration of the test drug until the secretory activity of the buccal and salivary glands returned to the control level. Subjects participating in a study of topical effect of expectorants must be cautioned not to swallow the drug since it may be absorbed and act systemically as well as topically. Similar techniques can be applied using patients with oral and pharyngeal pathologic states. The patient's subjective evalution of the effects of the drug must also be noted and recorded and relied upon for the assessment of expectorant activity.

2. *Selection of patients.* When patients are used as subjects, two categories of patient types may be selected. One patient type should be chosen for a cross-over study. This patient type should include subjects with a chronic condition, having a tendency to accumulate secretions in the mouth and throat due to chronic stomatitis, pharyngitis, and other conditions. The second patient type should include subjects with an acute inflammatory response, such as

pharyngitis, tonsillitis, stomatitis, or other oral disease, which produces viscous secretions necessitating the use of an expectorant. Because the production of secretions may be influenced by the diseased state of various organ systems, such as the circulatory, nervous system, or gastrointestinal system, patients with heart failure, renal and other diseases, must be excluded. All efforts should be made to maintain the same relative state of hydration throughout the study using intravenous fluids, if necessary. Patients should not be taking drugs that may affect the secretion of sputum or saliva, such as the anticholinergics, cholinergics, or antihistamines. Nonsmokers are preferable as subjects, but if smokers are used they must have abstained from smoking for at least 24 hours. The impact that environmental factors, such as temperature, humidity, and degree of air pollution might have on secretory activity should be recognized and controlled. As many variable factors as possible should be eliminated.

3. *Methods of study.* The double-blind, cross-over design may be used in patients with chronic oral or pharyngeal diseases accompanied by exudates and secretions. Suitable baseline studies must be performed over a selected period of time, prior to the administration of the test drugs. During this period, the following subjective responses should be noted: ease of expectoration, sensation experienced, effect on symptoms; objective responses such as volume, character of the fluid, color, viscosity, pH, and other parameters the investigator deems necessary should also be observed.

Following the baseline studies, similar observations should be made at appropriate time intervals after the administration of the drug and a placebo. The placebo must be indistinguishable from the test drug. Both are to be administered to subjects in a randomized fashion and at a dose and time sequence recommended in the labeling of the product for OTC use.

A randomized double-blind study, consisting of patients with acute pathologic processes with symptoms localized in the mouth and throat, should also be used. Patients with similar lesions should be considered in groups. The drug and the placebo should be applied in a dose and at a time sequence recommended for a minimum of 3 days. Similar observations as discussed above must be made to evaluate effectiveness. The Panel is aware of the fact that controlled observations made during a prior baseline period might not be obtainable with this type model and that most of the data are subjective and that little or none of it is objective. Many more subjects would be needed in such a study. Individual patient diaries should be kept in which are recorded at the time observations are made, the type of symptoms, their duration and severity, time of observation, date, and other pertinent data. Adverse reactions should be noted. The type, symptoms, duration, treatment, and disposition of the subject should be noted.

4. *Interpretation of the data.* Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories. At least one of these three studies must be of the cross-over technique performed in patients with chronic disease of the oral cavity. Approximately 20 to 30 patients will be required for the cross-over study described above. Because of the marked variability in sputum production in acute oral or pharyngeal conditions, compared to that of chronic conditions, day-to-day observations must be made. Since spontaneous improvement of the symptoms is part of the natural history of the disease process, much larger number of patients, possibly 75 or more, must be studied in this group. The subjective indices to be evaluated can be scored and subjected to statistical analysis. A P value of 0.05 or less should be obtained. Ninety-five percent confidence level means acceptable as evidence of a drug effect when compared with a placebo. All data submitted to the FDA must present both favorable and unfavorable results.

5. *Evaluation of study.* Tests for safety of expectorant ingredients not reviewed by this Panel should involve the usual animal studies and observations in humans relevant to various organ systems, that is, cardiovascular, venous, etc., as described elsewhere. (See part II. paragraph C. above—Determination of Safety and Effectiveness.)

**Reference**

(1) Trotti, W., and J. Adriani, "A Comparison of the Antisecretory and Vagolytic Effects of the Belladonna Alkaloids and Certain Synthetic Parasympatholytic Drugs," *Surgery,* 44:515–519, 1958.

**List of Subjects in 21 CFR Part 356**

Over-the-counter drugs.

Therefore, under the Federal Food, Drug and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p) 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding new Part 356, to read as follows:

## PART 356—ORAL HEALTH CARE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

**Subpart A—General Provisions**

Sec.



**Subpart B—Active Ingredients**



**Subpart C [Reserved]**

**Subpart D—Labeling**



**Authority:** Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321)p), 352, 355, 371); secs.. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

### Subpart A—General Provisions

**§356.1 Scope.**

(a) An over-the-counter oral health care drug product in a form suitable for topical administration is generally recognied as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1.

(b) references in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

**§ 356.3 Definitions.**

As used in this part:

(a) *Oral health care duug.* A drug product applied topoically for the proper care of the mouth, including the temporary relief of symptons of the mouth and throat, for example, occasional minor sore throat or mouth soreness.

(b) *Anesthetic/analgesic.* A substance applied topically to an epithelial surface (e.g., skin or mucous membrane) that relieves pain without necessarily abolishing other sensations (analgesic) or a substance applied topically that completely blocks pain receptors resulting in a sensation of numbness and abolition of response to painful stimuli (anesthetic).

(c) *Antimicrobial agent.* A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction and contributes to claimed effects of the product in which it is included.

(d) *Astringent.* An agent that causes contraction of the tissues or arrest of secretions by coagulation of protéins on a cell surface.

(e) *Debriding agent.* An agent which causes the removal of foreign material or devitalized or contaminated tissue from or adjacent to a traumatic or infected lesion to expose surrounding healthy tissue.

(f) *Decongestant.* An agent that reduces congestion or swelling. In over-the-counter use on mucous membranes the term generally refers to adrenergic drugs that act by vasoconstriction.

(g) *Demulcent.* A bland, inert agent that soothes and relieves irritation of inflamed or abraded surfaces such as mucous membranes.

(h) *Expectorant.* An agent that promotes the expectoration (spitting) of mucus or of respiratory tract secretions by decreasing the viscosity.

(i) *Gargle.* A fluid, usually flavored or medicated or both, but not necessarily so, which is intended to be used to rinse or bathe the posterior part of the oral cavity, with the additional intent to expel mucus from the throat.

(j) *Mouthwash (rinse).* A solution used for rinsing the mouth, not necessarily for medicinal purposes.

(k) *Oral cavity (mouth).* The cavity of the mouth and associated structures, including the cheeks, palate, oral mucosa, glands where ducts open into it, the teeth, and the tongue.

## Subpart B—Active Ingredients

**§ 356.10 Anesthetic/analgesic active ingredients.**

The active ingredients of the product may consist of any of the following when used within the dosage limits established for each ingredient:

(a) Aspirin.
(b) Benzocaine.
(c) Benzyl alcohol.
(d) Dyclonine hydrochloride.
(e) Hexylresorcinol.
(f) Menthol.
(g) Phenol.
(h) Phenolate sodium.
(i) Salicyl alcohol.

**§ 356.11 Antimicrobial active ingredients. [Reserved]**

**§ 356.12 Astringent active ingredients.**

The active ingredients of the product may consist of any of the following when used within the dosage limits established for each ingredients:

(a) Alum.
(b) Zinc chloride.

**§ 356.14 Debriding agent active ingredients.**

The active ingredients of the product may consist of any of the following whenused within the dosage limits established for each ingredient:

(a) Carbamide peroxide.
(b) Hydrogen peroxide.
(c) Sodium bicarbonate.

**§ 356.15 Decongestant active ingredients. [Reserved]**

**§ 356.16 Demulcent active ingredients.**

The active ingredients of the product may consist of any of the following when used within the dosage limits established for each ingredient:

(a) Elm bark.
(b) Gelatin.
(c) Glycerin.
(d) Pectin.

**§ 356.17 Expectorant active ingredients. [Reserved]**

**§ 356.20 Permitted combinations of active ingredients.**

(a) An active ingredient identified in § 356.10, § 356.11, § 356.12, § 356.14, § 356.15, § 356.16, and § 356.17 may be combined with one or more active ingredients from the same section if each active ingredient is present in full therapeutic doses or subtherapeutic doses where a subtherapeutic dose is appropriate, only when there is a clear demonstration that there is an improvement of safety or enhanced effectiveness or both.

(b) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any antimicrobial active ingredient identified in § 356.11.

(c) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any astringent active ingredient identified in § 356.12.

(d) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any decongestant active ingredient identified in § 356.15.

(e) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any demulcent active ingredient identified in § 356.16.

(f) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any antimicrobial active ingredient identified in § 356.11 and with any astringent active ingredient identified in § 356.12.

(g) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any antimicrobial active ingredient identified in § 356.11 and with any decongestant active ingredient identified in §356.15.

(h) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any antimicrobial active ingredient identified in § 356.11 and with any demulcent active ingredient identified in § 356.16.

(i) Any antimicrobial active ingredient identified in § 356.11 may be combined with any astringent active ingredient identified in § 356.12.

(j) Any antimicrobial active ingredient identified in § 356.11 may be combined with any decongestant active ingredient identified in § 356.15.

(k) Any antimicrobial active ingredient identified in § 356.11 may be combined with any demulcent active ingredient identified in § 356.16.

## Subpart C [Reserved]

## Subpart D—Labeling

**§ 356.50 Labeling of anesthetic/analgesic drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as follows.

(1) For all products containing aspirin identified in § 356.10(a), the product is identified as an "oral health care analgesic."

(2) For all products containing an ingredient identified in § 356.10(b) through § 356.10(i), the product is identified an an "oral health care anesthetic" or as an "oral health care anesthetic/analgesic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "For the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.10.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing aspirin identified in § 356.10(a).* (i) "Do not use if you are sensitive or allergic to aspirin."

(ii) "Do not use if you have a bleeding problem or if you are taking an anticoagulant drug."

(iii) "Do not use without a physician's or dentist's advice if your mouth is highly irritated or ulcerated."

(iv) "Do not use after surgery in the mouth and throat."

(v) "Provide good fluid intake when aspirin or aspirin-containing preparations are used."

(3) *For products containing any ingredient identified in § 356.10 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing aspirin identified in § 356.10(a).* The topical dosage of aspirin is incorporated in a chewing gum base. Adults: chew 420 milligrams of aspirin as needed, not to exceed 3,360 milligrams in 24 hours. Children 6 to under 12 years of age: Chew 210 to 420 milligrams of aspirin as needed, not to exceed 1,680 milligrams in 24 hours. Children 3 to under 6 years of age: Chew 210 milligrams of aspirin as needed, not to exceed 630 milligrams in 24 hours. For children under 3 years of age, there is no recommended dosage except unduer the advice and supervision of a dentist or physician.

(2) *For products containing benzocaine identified in § 356.10(b).* Topical dosage for adults and children 3 years of age and older is a 5- to20-percent solution (spray) or gel used not more than three to four times daily or a lozenge containing 2 to 15 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(3) *For products containing benzyl alcohol identified in § 356.10(c).* Topical dosage for adults and children 3 years of age and older is a 0.05- to 10-percent solution (rinse, mouthwash, spray, or drops) used not more than three to four times daily or a lozenge containing 100 to 500 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *For products containing dyclonine hydrochloride identified in § 356.10(d).* Topical dosage for adults and children 3 years of age and older is a 0.05- to 0.10-percent solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 1 to 3 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(5) *For products containing hexylresorcinol identified in § 356.10(e).* Topical dosage for adults and children 3 years of age and older is a 0.05- to 0.1-percent solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 2 to 4 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(6) *For products containing menthol identified in § 356.10(f).* Topical dosage for adults and children 3 years of age and older is a 0.04- to 2.0-percent solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 2 to 20 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(7) *For products containing phenol identified in § 356.10(g).* Topical dosage for adults and children 3 years of age and older is a 0.5- to 1.5-percent aqueous solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 10 to 50 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(8) *For products containing phenolate sodium identified in § 356.10(h).* Topical dosage for adults and children 3 years of age and older is an aqueous solution (rinse, mouthwash, gargle, or spray) containing phenolate sodium equivalent to 0.5 to 1.5 percent phenol used not more than three to four times daily or a lozenge containing phenolate sodium equivalent to 10 to 50 milligrams of phenol taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(9) *For products containing salicyl alcohol identified in § 356.10(i).* Topical dosage for adults and children 3 years of age and older is a 1- to 6-percent aqueous solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 50 to 100 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

**§ 356.51 Labeling of antimicrobial drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care antimicrobial."

(b) *Indications.* [Reserved]

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.11.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.11 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* [Reserved]

**§ 356.52 Labeling of astrigent drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care astringent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "Aids in the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat.

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.12.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.12 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing alum identified in § 356.12(a).* Topical dosage for adults and children 3 years of age and older is a 0.2- to 0.5-percent aqueous solution (rinse, gargle, or spray) or swab used not more than three to four time daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(2) *For products containing zinc chloride identified in § 356.12(b).* Topical dosage for adults and children 3 years of age and older is a 0.1- to 0.25-percent solution (rinse or mouthwash) or swab used three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

**§ 356.54 Labeling of debriding agent drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care debriding agent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "Aids in the removal of phlegm, mucus, or other secretions in the temporary relief of discomfort due to occasional sore throat and sore mouth."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.14.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to childen under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.14 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* The labeling of the products contains the following information under the heading "Directions."

(1) *For products containing carbamide peroxide identified in § 356.14(a).* Topical dosage for adults and children 3 years of age and older is a solution (rinse, gargle, or spray) containing 10 to 15 percent carbamide peroxide in anhydrous glycerin or water used not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(2) *For products containing hydrogen peroxide identified in § 356.14(b).* Topical dosage for adults and children 3 years of age and older is a solution (rinse, mouthwash, gargle, or spray) containing hydrogen peroxide (3 percent) diluted with an equal part of water or swab used not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(3) *For products containing sodium bicarbonate identified in § 356.14(c).* Topical dosage for adults and children 3 years of age and older is a solution (gargle) prepared by combining 5 to 10 percent sodium bicarbonate with one-half teaspoonful of sodium chloride (table salt) in a glass (8 ounces) of warm water used not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

**§ 356.55 Labeling of decongestant drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care decongestant."

(b) *Indications.* [Reserved]

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.15.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.15 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* [Reserved]

**§ 356.56 Labeling of demulcent drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care demulcent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "Aids in the temporary relief of minor discomfort and protects irritated areas in sore mouth and sore throat."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.16.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.16 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(3) *For products containing glycerin identified in § 356.16(c).* "Do not use full strength. Dilute with two or three volumes of water."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing elm bark identified in § 356.16(a).* Topical dosage for adults and children 3 years of age and older is a lozenge (agar or water-soluble gum base) containing 10 to 15 percent elm bark taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(2) *For products containing gelatin identified in § 356.16(b).* Topical dosage for adults and children 3 years of age and older is a 5- to 10-percent aqueous solution (rinse, gargle, or spray), swab, or lozenge or gel containing a sufficient quantity to form a solid or semisolid state used as often as necessary. For children under 3 years of age, there is no recommended dosage except under the advice of a dentist or physician.

(3) *For products containing glycerin identified in § 356.16(c).* Topical dosage for adults and children 3 years of age and older is a solution (rinse, mouthwash, or spray) or swab containing glycerin diluted with 2 or 3 parts of water used as often as necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *For products containing pectin identified in § 356.16(d).* Topical dosage for adults and children 3 years of age and older is a solution (rinse, gargle, or spray), swab, or lozenge or gel in quantities sufficient to form a solid or semisolid state, used as often as necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

**§ 356.57 Labeling of expectorant drug products.**

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care expectorant."

(b) *Indications.* [Reserved]

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.17.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.17 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

Interested persons may, on or before August 23, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before September 22, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 31, 1982.

**Mark Novitch,**

*Acting Commissioner of Food and Drugs.*

Dated: May 13, 1982.

**Richard S. Schweiker,**

*Secretary of Health and Human Services.*

[FR Doc. 82–13835 Filed 5–24–82; 8:45 am]

BILLING CODE 4160–01–M

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## AGENCY PUBLICATION ON ASSIGNED DAYS OF THE WEEK

The following agencies have agreed to publish all documents on two assigned days of the week (Monday/Thursday or Tuesday/Friday). This is a voluntary program. (See OFR NOTICE 41 FR 32914, August 6, 1976.)

| Monday | Tuesday | Wednesday | Thursday | Friday |
|---|---|---|---|---|
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| DOT/COAST GUARD | USDA/FNS | | DOT/COAST GUARD | USDA/FNS |
| DOT/FAA | USDA/REA | | DOT/FAA | USDA/REA |
| DOT/FHWA | USDA/SCS | | DOT/FHWA | USDA/SCS |
| DOT/FRA | MSPB/OPM | | DOT/FRA | MSPB/OPM |
| DOT/MA | LABOR | | DOT/MA | LABOR |
| DOT/NHTSA | HHS/FDA | | DOT/NHTSA | HHS/FDA |
| DOT/RSPA | | | DOT/RSPA | |
| DOT/SLSDC | | | DOT/SLSDC | |
| DOT/UMTA | | | DOT/UMTA | |

Documents normally scheduled for publication on a day that will be a Federal holiday will be published the next work day following the holiday. Comments on this program are still invited.

Comments should be submitted to the Day-of-the-Week Program Coordinator, Office of the Federal Register, National Archives and Records Service, General Services Administration, Washington, D.C. 20408.

## List of Public Laws

**Last Listing May 19, 1982**

This is a continuing list of public bills from the current session of Congress which have become Federal laws. The text of laws is not published in the **Federal Register** but may be ordered in individual pamphlet form (referred to as "slip laws") from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 (telephone 202–275–3030).

**S. 1131 / Public Law 97–177** Prompt Payment Act. (May 21, 1982; 96 Stat. 85) Price: $1.75

**H.J. Res. 412 / Public Law 97–178** To authorize and request the President to designate May 20, 1982, as "Amelia Earhart Day". (May 21, 1982; 96 Stat. 89) Price: $1.75